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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions.



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## **INHIBITORS OF HISTONE DEACETYLASE**

### **BACKGROUND OF THE INVENTION**

#### *Field of the Invention*

**[0001]** This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

#### *Summary of the Related Art*

**[0002]** In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

**[0003]** Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the  $\alpha,\epsilon$ -amino groups of N-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science*, **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

**[0004]** Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**: 4868-4873 (1999), teaches that HDACs is divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao *et al.*, *Genes & Dev.*, **14**: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, *FEBS*, **478**: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs.

**[0005]** Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, **177**: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G<sub>1</sub> and G<sub>2</sub> phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin *et al.*, *Nature*, **401**: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.*, U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme *et al.*, WO 01/38322 and PCT IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

**[0006]** The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**:4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC-1, HDAC-2, and HDAC-3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC-4, HDAC-5, and HDAC-6, which are members of the second class of HDACs. Kao *et al.*, *Gene & Development* **14**:55-66 (2000), discloses an additional member of this second class, called HDAC-7. More recently, Hu, E. *et al.* *J. Bio. Chem.* **275**:15254-13264 (2000) discloses the newest member of the first class of histone deacetylases, HDAC-8. It has been unclear what roles these individual HDAC enzymes play.

**[0007]** These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

#### **BRIEF SUMMARY OF THE INVENTION**

**[0008]** The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

**[0009]** In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

**[0010]** In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

**[0011]** In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

**[0012]** The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

**[0013]** Figure 1 is a graph showing the antitumor activity of compound **106** in an HCT 116 human colorectal tumor model.

**[0014]** Figures 2-11 show additional data for other compounds used in the *in vivo* experiment described in Assay Example 2.

### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

**[0015]** The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

**[0016]** For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

**[0017]** As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the  $\epsilon$ -amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6,



HDAC-7, and HDAC-8. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

**[0018]** The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

**[0019]** Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

**[0020]** For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (e.g.  $\text{CH}_3\text{-CH}_2\text{-}$ ), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g.,  $\text{-CH}_2\text{-CH}_2\text{-}$ ), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as  $(\text{A})_a\text{-B-}$ , wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure.

**[0021]** The term “hydrocarbonyl” refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A “C<sub>0</sub>” hydrocarbonyl is used to refer to a covalent bond. Thus, “C<sub>0</sub>-C<sub>3</sub>-hydrocarbonyl” includes a covalent bond, methyl, ethyl, propyl, and cyclopropyl.

**[0022]** The term “alkyl” as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A “C<sub>0</sub>” alkyl (as in “C<sub>0</sub>-C<sub>3</sub>-alkyl”) is a covalent bond (like “C<sub>0</sub>” hydrocarbonyl).

**[0023]** The term “alkenyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

**[0024]** The term “alkynyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

**[0025]** An “alkylene,” “alkenylene,” or “alkynylene” group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

**[0026]** The term “cycloalkyl” as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

**[0027]** The term “heteroalkyl” refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

**[0028]** An "aryl" group is a C<sub>6</sub>-C<sub>14</sub> aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C<sub>6</sub>-C<sub>10</sub> aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C<sub>1</sub>-C<sub>6</sub>)alk(C<sub>6</sub>-C<sub>10</sub>)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

**[0029]** A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. The heterocyclic group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

**[0030]** As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14  $\pi$  electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroaralkyl groups comprise a C<sub>1</sub>-C<sub>6</sub> alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolyethyl, thiazolylmethyl, and thiazolyethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

**[0031]** An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

**[0032]** Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

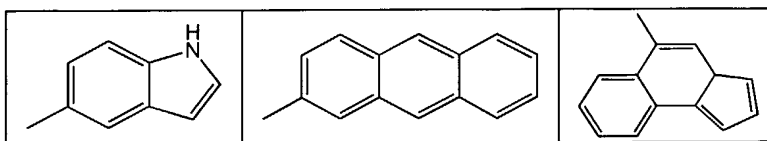
**[0033]** As employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,
- (b) C<sub>1</sub>-C<sub>5</sub> alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> alkoxy carbonyl, aryloxy carbonyl, C<sub>2</sub>-C<sub>8</sub> acyl, C<sub>2</sub>-C<sub>8</sub> acylamino, C<sub>1</sub>-C<sub>8</sub> alkylthio, arylalkylthio, arylthio, C<sub>1</sub>-C<sub>8</sub> alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C<sub>1</sub>-C<sub>8</sub>

alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C<sub>0</sub>-C<sub>6</sub> N-alkyl carbamoyl, C<sub>2</sub>-C<sub>15</sub> N,N-dialkylcarbamoyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C<sub>3</sub>-C<sub>7</sub> heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

- (c)  $-(CH_2)_s-NR^{30}R^{31}$ , wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R<sup>30</sup> and R<sup>31</sup> are each independently hydrogen, cyano, oxo, carboxamido, amidino, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub> alkylaryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> alkoxycarbonyl, aryloxycarbonyl, aryl-C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl, C<sub>2</sub>-C<sub>8</sub> acyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or R<sup>30</sup> and R<sup>31</sup> taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

**[0034]** In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 10-12 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes the following:



**[0035]** A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

**[0036]** The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (i.e., R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (i.e., NH<sub>2</sub>-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom.

The term "amino" is meant to include  $\text{NH}_2$ , alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

**[0037]** The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

**[0038]** A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes ( $-\text{CH}_2-$ ) substituted with oxygen to form carbonyl ( $-\text{CO}-$ ).

**[0039]** An "unsubstituted" moiety as defined above (e.g., unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

**[0040]** Preferred embodiments of a particular genus of compounds of the invention include combinations of preferred embodiments. For example, paragraph [0042] identifies a preferred  $\text{Ay}^1$  and paragraph [0046] identifies preferred  $\text{Ar}^1$  (both for compound (1) of paragraph [0041]). Thus, another preferred embodiment includes those compounds of formula (1) in paragraph [0041] in which  $\text{Ay}^1$  is as defined in paragraph [0042] and  $\text{Ar}^1$  is as defined in paragraph [0046].

## Compounds

**[0041]** In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):



and pharmaceutically acceptable salts thereof, wherein

$\text{R}^3$  and  $\text{R}^4$  are independently selected from the group consisting of hydrogen,  $\text{L}^1$ ,  $\text{Cy}^1$ , and  $-\text{L}^1-$   
 $\text{Cy}^1$ , wherein

$\text{L}^1$  is  $\text{C}_1$ - $\text{C}_6$  alkyl,  $\text{C}_2$ - $\text{C}_6$  heteroalkyl, or  $\text{C}_3$ - $\text{C}_6$  alkenyl; and

Cy<sup>1</sup> is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

R<sup>3</sup> and R<sup>4</sup> are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally forms part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y<sup>1</sup> is selected from the group consisting of -N(R<sup>1</sup>)(R<sup>2</sup>), -CH<sub>2</sub>-C(O)-N(R<sup>1</sup>)(R<sup>2</sup>), halogen, and hydrogen, wherein

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, L<sup>1</sup>, Cy<sup>1</sup>, and -L<sup>1</sup>-Cy<sup>1</sup>, wherein

L<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> heteroalkyl, or C<sub>3</sub>-C<sub>6</sub> alkenyl; and

Cy<sup>1</sup> is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

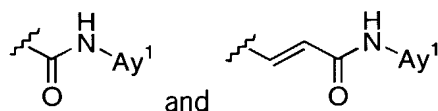
R<sup>1</sup> and R<sup>2</sup> are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally may form part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y<sup>2</sup> is a chemical bond or N(R<sup>0</sup>), where R<sup>0</sup> is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

Ar<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>1</sub>-C<sub>6</sub>-heteroalkylene (preferably, in which one -CH<sub>2</sub>- is replaced with -NH-, and more preferably -NH-CH<sub>2</sub>-), C<sub>2</sub>-C<sub>6</sub> alkenylene or C<sub>2</sub>-C<sub>6</sub> alkynylene;

Ar<sup>1</sup> is arylene or heteroarylene, either of which optionally is substituted; and

Z<sup>1</sup> is selected from the group consisting of



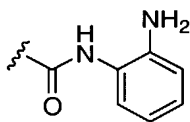
wherein  $Ay^1$  is aryl or heteroaryl, which optionally is substituted.

**[0042]** Preferably in the compounds according to paragraph [0041],  $Ay^1$  is phenyl or thienyl, each substituted with -OH or -NH<sub>2</sub>.

**[0043]** More preferably in the compounds according to paragraph [0041],  $Ay^1$  is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which  $Ay^2$  is attached.

**[0044]** More preferably in the compounds according to paragraph [0041],  $Ay^1$  is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

**[0045]** In some preferred embodiments of the compounds according to paragraph [0041],  $Z^1$  is



**[0046]** In some preferred embodiments of the compounds according to paragraph [0041],  $Ar^1$  is phenylene. In some embodiments,  $Ar^1$  is alkylene, preferably methylene. In some preferred embodiments,  $Y^2$  is -NH-. In some preferred embodiments,  $Y^1$  is -N(R<sup>1</sup>)(R<sup>2</sup>) or -CH<sub>2</sub>-C(O)-N(R<sup>1</sup>)(R<sup>2</sup>).

**[0047]** In some embodiments of the compounds according to paragraph [0041], R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of hydrogen, L<sup>1</sup>, Cy<sup>1</sup>, and -L<sup>1</sup>-Cy<sup>1</sup>. In some embodiments, R<sup>1</sup> and/or R<sup>2</sup> is hydrogen. In other embodiments, R<sup>1</sup> and/or R<sup>2</sup> is alkyl or alkenyl, preferably allyl. In still other embodiments, R<sup>1</sup> and/or R<sup>2</sup> is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R<sup>1</sup> and/or R<sup>2</sup> is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

**[0048]** In some embodiments of the compounds according to paragraph [0041], R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, L<sup>1</sup>, Cy<sup>1</sup>, and -L<sup>1</sup>-Cy<sup>1</sup>. In some embodiments, R<sup>3</sup> and/or R<sup>4</sup> is hydrogen. In other embodiments, R<sup>3</sup> and/or R<sup>4</sup> is alkyl or alkenyl, preferably allyl. In still other embodiments, R<sup>3</sup> and/or R<sup>4</sup> is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings.

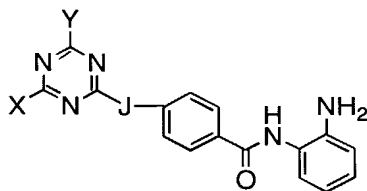


Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R<sup>3</sup> and/or R<sup>4</sup> is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

**[0049]** As set forth above, L<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> heteroalkyl, or C<sub>3</sub>-C<sub>6</sub> alkenyl. However, one skilled in the art will understand that when L<sup>1</sup> is not a terminal group, then L<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> heteroalkylene, or C<sub>3</sub>-C<sub>6</sub> alkenylene. In some embodiments, L<sup>1</sup> is alkylene, preferably methylene or ethylene. In other embodiments, L<sup>1</sup> is alkenyl, preferably allyl. In some embodiments, Cy<sup>1</sup> is the radical of a heterocyclic group including, without limitation, piperidine, pyrrolidine, piperazine, and morpholine, each of which optionally is substituted and optionally is fused to one or more aryl rings. In other embodiments Cy<sup>1</sup> is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl. In still other embodiments, Cy<sup>1</sup> is aryl or heteroaryl, e.g., phenyl, pyridyl, or pyrrolyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy<sup>1</sup> is fused to one or two benzene rings. In some embodiments, Cy<sup>1</sup> has between one and about five substituents selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and halo. Examples of preferred substituents include methyl, methoxy, and fluoro.

**[0050]** In some embodiments of the compounds according to paragraph [0041], R<sup>1</sup> and R<sup>2</sup> and/or R<sup>3</sup> and R<sup>4</sup> are taken together with the adjacent nitrogen atom to form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring optionally is substituted, and optionally is fused to one or more aryl rings. In some preferred embodiments, R<sup>1</sup> and R<sup>2</sup> and/or R<sup>3</sup> and R<sup>4</sup> are taken together with the adjacent nitrogen atom to form a ring such as, for example, pyrrolidine, piperidine, piperazine, and morpholine, wherein the ring optionally is substituted, and optionally is fused to an aryl ring. In some embodiments, the ring comprising R<sup>1</sup> and R<sup>2</sup> or R<sup>3</sup> and R<sup>4</sup> is fused to a benzene ring. In some embodiments, the ring comprising R<sup>1</sup> and R<sup>2</sup> or R<sup>3</sup> and R<sup>4</sup> has a substituent comprising an aryl or cycloalkyl ring, either of which optionally is substituted and optionally is fused to a cycloalkyl, aryl, heteroaryl, or heterocyclic ring. Preferred substituents include, without limitation, phenyl, phenylmethyl, and phenylethyl, the phenyl ring of which optionally is fused to a cycloalkyl, aryl, or heterocyclic ring.

**[0051]** In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of formula 1(a):



(1a)

and pharmaceutically acceptable salts thereof, wherein

J is C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, -N(R<sup>20</sup>)-, -N(R<sup>20</sup>)-CH<sub>2</sub>-, -O-, or -O-CH<sub>2</sub>-;

R<sup>20</sup> is -H or -Me;

X and Y are independently selected from -NH<sub>2</sub>, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A-(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>n</sub>-B-;

A is H, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -O-, or a direct bond; and

n is 0 (in which case A is directly bonded to B) or 1.

**[0052]** Preferably in the compounds according to paragraph [0051], A is phenyl optionally substituted with one or more moieties selected from halo (preferably chloro) and methoxy, and B is -NH-. In another preferred embodiment, A is selected from cyclopropyl, pyridinyl, and indanyl.


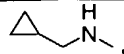
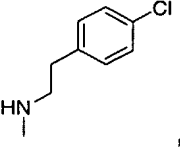
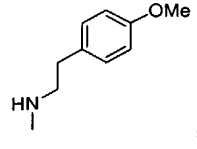
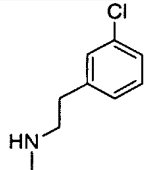
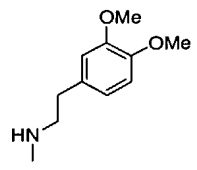
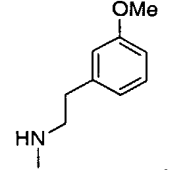
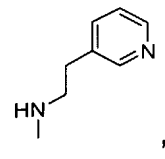
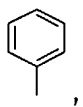
**[0053]** Preferably in the compounds according to paragraph [0051], J is -NH-CH<sub>2</sub>-, -O-CH<sub>2</sub>-, -N(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH=CH-, or -CH<sub>2</sub>-CH<sub>2</sub>-.

**[0054]** Preferably in the compounds according to paragraph [0051], R<sup>20</sup> is -H.

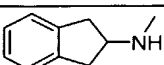
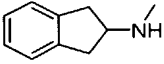
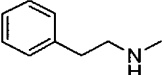
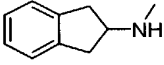
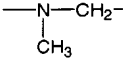
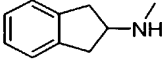
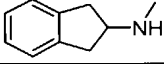

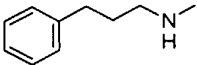
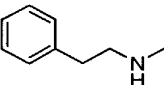

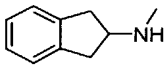
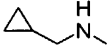
**[0055]** In the compounds according to paragraph [0051] X is preferably selected from

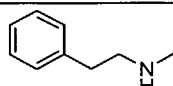
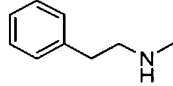

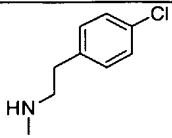

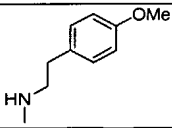

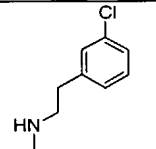

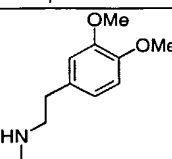

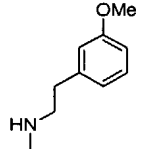
|     |                  |       |  |
|-----|------------------|-------|--|
|     |                  |       |  |
|     |                  | -OMe, |  |
|     | -NH <sub>2</sub> |       |  |
|     |                  |       |  |
| and |                  |       |  |

and Y is preferably selected from

|   |   |  |   |
|---|---|--|---|
| -NH <sub>2</sub> ,  |  |   | n-BuNH,   |
| MeOCH <sub>2</sub> CH <sub>2</sub> NH,  |  |  |  |
|  |  |  |  |
| -H  | Me  | -OMe   | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> NH-                                 |
| and   | CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> NH-                              |  |   |

[0056] In a more preferred embodiment of the compounds according to paragraph [0051], the HDAC inhibitors of the invention comprise the following compounds of formula 1a:

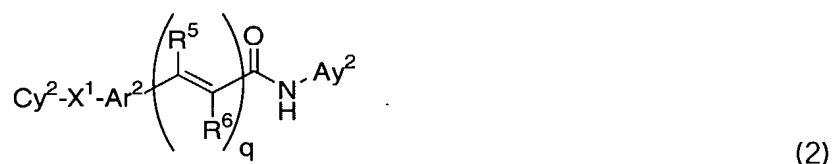
| Cpd | J   | X   | Y   |
|-----|---|---|---|
| 204 | -NH-  |    | -NH <sub>2</sub>  |
| 207 | -OCH <sub>2</sub> -   |    | -NH <sub>2</sub>  |
| 210 | -NHCH <sub>2</sub> -  |  | -H  |
| 212 | -NHCH <sub>2</sub> -  | -OMe  | -OMe  |
| 214 | -NHCH <sub>2</sub> -  |  | -OMe  |
| 216 |  |  | -Me   |
| 218 | -NHCH <sub>2</sub> -  |  | -Me   |
| 220 | -CH=CH-   | -NH <sub>2</sub>  | -NH <sub>2</sub> -  |
| 223 | -CH=CH-   |  | -NH <sub>2</sub>  |
| 224 | -CH <sub>2</sub> CH <sub>2</sub> -  | -NH <sub>2</sub>  | -NH <sub>2</sub>  |
| 470 | -NHCH <sub>2</sub> -  |  | NH <sub>2</sub>   |
| 471 | -NHCH <sub>2</sub> -  |  |  |
| 472 | -NHCH <sub>2</sub> -  |  |  |

| Cpd | J                    | X   | Y   |
|-----|----------------------|---|---|
| 473 | -NHCH <sub>2</sub> - |    | n-BuNH  |
| 474 | -NHCH <sub>2</sub> - |   | MeO(CH <sub>2</sub> ) <sub>2</sub> NH   |
| 475 | -NHCH <sub>2</sub> - |  |  |
| 476 | -NHCH <sub>2</sub> - |  |  |
| 477 | -NHCH <sub>2</sub> - |  |  |
| 478 | -NHCH <sub>2</sub> - |  |  |
| 479 | -NHCH <sub>2</sub> - |  |  |

| Cpd | J                    | X | Y |
|-----|----------------------|---|---|
| 480 | -NHCH <sub>2</sub> - |   |   |
| 481 | -NHCH <sub>2</sub> - |   |   |
| 482 | -NHCH <sub>2</sub> - |   |   |

| Cpd | J                    | X | Y               |
|-----|----------------------|---|-----------------|
| 483 | -NHCH <sub>2</sub> - |   | Me              |
| 484 | -NHCH <sub>2</sub> - |   | NH <sub>2</sub> |
| and |                      |   |                 |
| 485 | -NHCH <sub>2</sub> - |   |                 |

**[0057]** In a second aspect, the novel histone deacetylase inhibitors of the invention are represented by formula (2):



and pharmaceutically acceptable salts thereof, wherein

Cy<sup>2</sup> is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X<sup>1</sup> is selected from the group consisting of a covalent bond, M<sup>1</sup>-L<sup>2</sup>-M<sup>1</sup>, and L<sup>2</sup>-M<sup>2</sup>-L<sup>2</sup> wherein

L<sup>2</sup>, at each occurrence, is independently selected from the group consisting of a chemical bond, C<sub>1</sub>-C<sub>4</sub> alkylene, C<sub>2</sub>-C<sub>4</sub> alkenylene, and C<sub>2</sub>-C<sub>4</sub> alkynylene, provided that L<sup>2</sup> is not a chemical bond when X<sup>1</sup> is M<sup>1</sup>-L<sup>2</sup>-M<sup>1</sup>;

M<sup>1</sup>, at each occurrence, is independently selected from the group consisting of -O-, -N(R<sup>7</sup>)-, -S-, -S(O)-, S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(R<sup>7</sup>)-, -N(R<sup>7</sup>)-S(O)<sub>2</sub>-, -C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-O- and -O-C(O)-NH-, wherein R<sup>7</sup> is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

M<sup>2</sup> is selected from the group consisting of M<sup>1</sup>, heteroarylene, and heterocyclylene, either of which rings optionally is substituted;

Ar<sup>2</sup> is arylene or heteroarylene, each of which is optionally substituted;

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

q is 0 or 1; and

Ay<sup>2</sup> is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which Ay<sup>2</sup> is attached) and further optionally substituted;

provided that when Cy<sup>2</sup> is naphthyl, X<sup>1</sup> is -CH<sub>2</sub>-, Ar<sup>2</sup> is phenyl, R<sup>5</sup> and R<sup>6</sup> are H, and q is 0 or 1, Ay<sup>2</sup> is not phenyl or o-hydroxyphenyl.

**[0058]** In a preferred embodiment of the compounds according to paragraph [0057], when Ay<sup>2</sup> is o-phenol optionally substituted by halo, nitro, or methyl, Ar<sup>2</sup> is optionally substituted phenyl, X<sup>1</sup> is -O-, -CH<sub>2</sub>-, -S-, -S-CH<sub>2</sub>-, -S(O)-, -S(O)<sub>2</sub>-, -C(O)-, or -OCH<sub>2</sub>-, then Cy<sup>2</sup> is not optionally substituted phenyl or naphthyl.

**[0059]** In another preferred embodiment of the compounds according to paragraph [0057], when Ay<sup>2</sup> is o-anilinyll optionally substituted by halo, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy or -NO<sub>2</sub>, q is 0, Ar<sup>2</sup> is phenyl, and X<sup>1</sup> is -CH<sub>2</sub>-, then Cy<sup>2</sup> is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).

**[0060]** In another preferred embodiment of the compounds according to paragraph [0057], when X<sup>1</sup> is -CH<sub>2</sub>-, Ar<sup>2</sup> is optionally substituted phenyl, q is 1, and R<sup>6</sup> is H, then Cy<sup>2</sup> is not optionally substituted imidazole.

**[0061]** In another preferred embodiment of the compounds according to paragraph [0057], when Ar<sup>2</sup> is amino or hydroxy substituted phenyl, X<sup>1</sup> is C<sub>0</sub>-C<sub>8</sub>-alkyl-X<sup>1a</sup>- C<sub>0</sub>-C<sub>8</sub>-alkyl, wherein X<sup>1a</sup> is -CH<sub>2</sub>-, -O-, -S-, -NH-, -C(O)-, then Cy<sup>2</sup> is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.

**[0062]** In another preferred embodiment of the compounds according to paragraph [0057], when Ay<sup>2</sup> is o-phenol, Ar<sup>2</sup> is substituted phenyl, X<sup>1</sup> is -O-, -S-, -CH<sub>2</sub>-, -O-CH<sub>2</sub>-, -S-CH<sub>2</sub>-, or -C(O)-, and R<sup>5</sup> and R<sup>6</sup> are H, then Cy<sup>2</sup> is not optionally substituted naphthyl.

**[0063]** In another preferred embodiment of the compounds according to paragraph [0057], when Ay<sup>2</sup> is o-anilinyll, q is 0, Ar<sup>2</sup> is unsubstituted phenyl, X<sup>1</sup> is -CH<sub>2</sub>-, then Cy<sup>2</sup> is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.

**[0064]** Preferably in the compounds according to paragraph [0057], Ay<sup>2</sup> is phenyl or thienyl, each substituted with -OH or -NH<sub>2</sub>.

**[0065]** More preferably in the compounds according to paragraph [0057], Ay<sup>2</sup> is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay<sup>2</sup> is attached.

**[0066]** More preferably in the compounds according to paragraph [0057],  $Ay^2$  is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

**[0067]** In a another embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0057] wherein

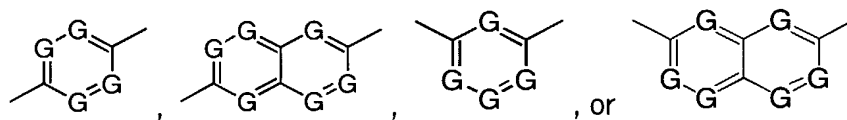
q is 1;

$M^1$ , at each occurrence, is selected from the group consisting of  $-N(R^7)-$ ,  $-S-$ ,  $-C(O)-NH-$ , and  $-O-C(O)-NH-$ , where  $R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and

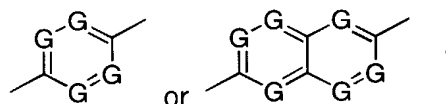
$Ay^2$  is aniliny, which optionally is substituted.

**[0068]** In some preferred embodiments of the compounds according to paragraph [0067], the  $-NH_2$  group of  $Ay^2$  is in an ortho position with respect to the nitrogen atom to which  $Ay^2$  is attached. In some embodiments,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen and  $C_1$ - $C_4$  alkyl. In some preferred embodiments,  $R^5$  and  $R^6$  are hydrogen.

**[0069]** In some embodiments of the compounds according to paragraph [0067],  $Ar^2$  has the formula



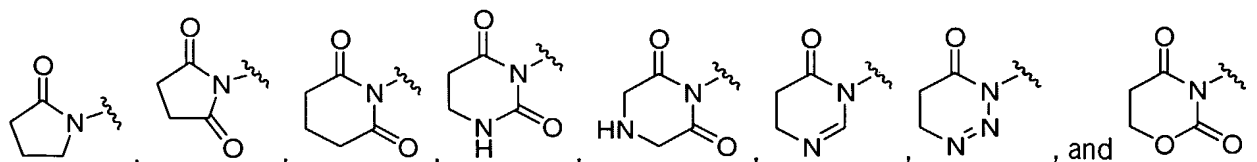
wherein G, at each occurrence, is independently N or C, and C optionally is substituted. In some preferred embodiments,  $Ar^2$  has the formula



**[0070]** In some preferred embodiments of the compounds according to paragraph [0069],  $Ar^2$  is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolyne.

**[0071]** In some embodiments of the compounds according to paragraph [0067],  $X^1$  is a chemical bond. In some embodiments,  $X^1$  is  $L^2-M^2-L^2$ , and  $M^2$  is selected from the group consisting of  $-NH-$ ,  $-N(CH_3)-$ ,  $-S-$ ,  $-C(O)-N(H)-$ , and  $-O-C(O)-N(H)-$ . In some embodiments,  $X^1$  is  $L^2-M^2-L^2$ , where at least one occurrence of  $L^2$  is a chemical bond. In other embodiments,  $X^1$  is  $L^2-M^2-L^2$ , where at least one occurrence of  $L^2$  is alkylene, preferably methylene. In still other embodiments,  $X^1$  is  $L^2-M^2-L^2$ , where at least one occurrence of  $L^2$  is alkenylene. In some embodiments,  $X^1$  is  $M^1-L^2-M^1$  and  $M^1$  is selected from the group consisting of  $-NH-$ ,  $-N(CH_3)-$ ,  $-S-$ , and  $-C(O)-N(H)-$ .

**[0072]** In some embodiments of the compounds according to paragraph [0067], Cy<sup>2</sup> is aryl or heteroaryl, e.g., phenyl, pyridyl, imidazolyl, or quinolyl, each of which optionally is substituted. In some embodiments, Cy<sup>2</sup> is heterocyclyl, e.g.,



each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy<sup>2</sup> has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl.

**[0073]** In a preferred embodiment of the compounds of paragraph [0057], the invention comprises compounds of structural formula (2a):



and pharmaceutically acceptable salts thereof, wherein

Ar<sup>a</sup> is phenyl or thienyl;

R<sup>6</sup> is H, or C<sub>1</sub>-C<sub>6</sub>-alkyl (preferably -CH<sub>3</sub>);

Y and Z are independently -CH= or -N=;

W is halo, (V'-L<sup>4</sup>)<sub>t</sub>-V-L<sup>3</sup>;

L<sup>3</sup> is a direct bond, -C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl, -(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)<sub>m1</sub>-X'-(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)<sub>m2</sub>, -NH-(C<sub>0</sub>-C<sub>3</sub>-hydrocarbyl), (C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)-NH-, or -NH-(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)-NH-;

m<sub>1</sub> and m<sub>2</sub> are independently 0 or 1;

X' is -N(R<sup>21</sup>)-, -C(O)N(R<sup>21</sup>)-, N(R<sup>21</sup>)C(O)-, -O-, or -S-;

R<sup>21</sup> is -H, V''-(C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>c</sub>;

L<sup>4</sup> is (C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>a</sub>-M-(C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>b</sub>;

a and b are independently 0 or 1;

M is -NH-, -NHC(O)-, -C(O)NH-, -C(O)-, -SO<sub>2</sub>-, -NHSO<sub>2</sub>-, or -SO<sub>2</sub>NH-

V, V', and V'' are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the  $\mathcal{A}$  and  $\text{Ar}^a$  rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

**[0074]** In a preferred embodiment of the compound according to paragraph [0073]:

Y and Z are  $-\text{CH}=\text{}$  and  $\text{R}^6$  is H;

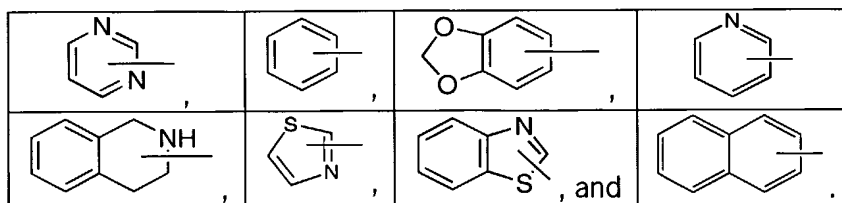
W is  $\text{V-L}^3$ ;

$\text{L}^3$  is  $-\text{NH-CH-}$  or  $-\text{CH-NH-}$ ;

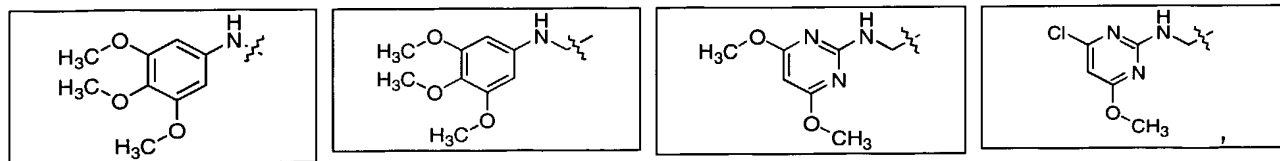
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy,  $\text{C}_1\text{-C}_6\text{-hydrocarbyl}$ ,  $\text{C}_1\text{-C}_6\text{-hydrocarbyl-oxy}$  or  $-\text{thio}$  (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

$\text{Ar}^a$  is phenyl and the amino moieties to which it is bound are ortho to each other.

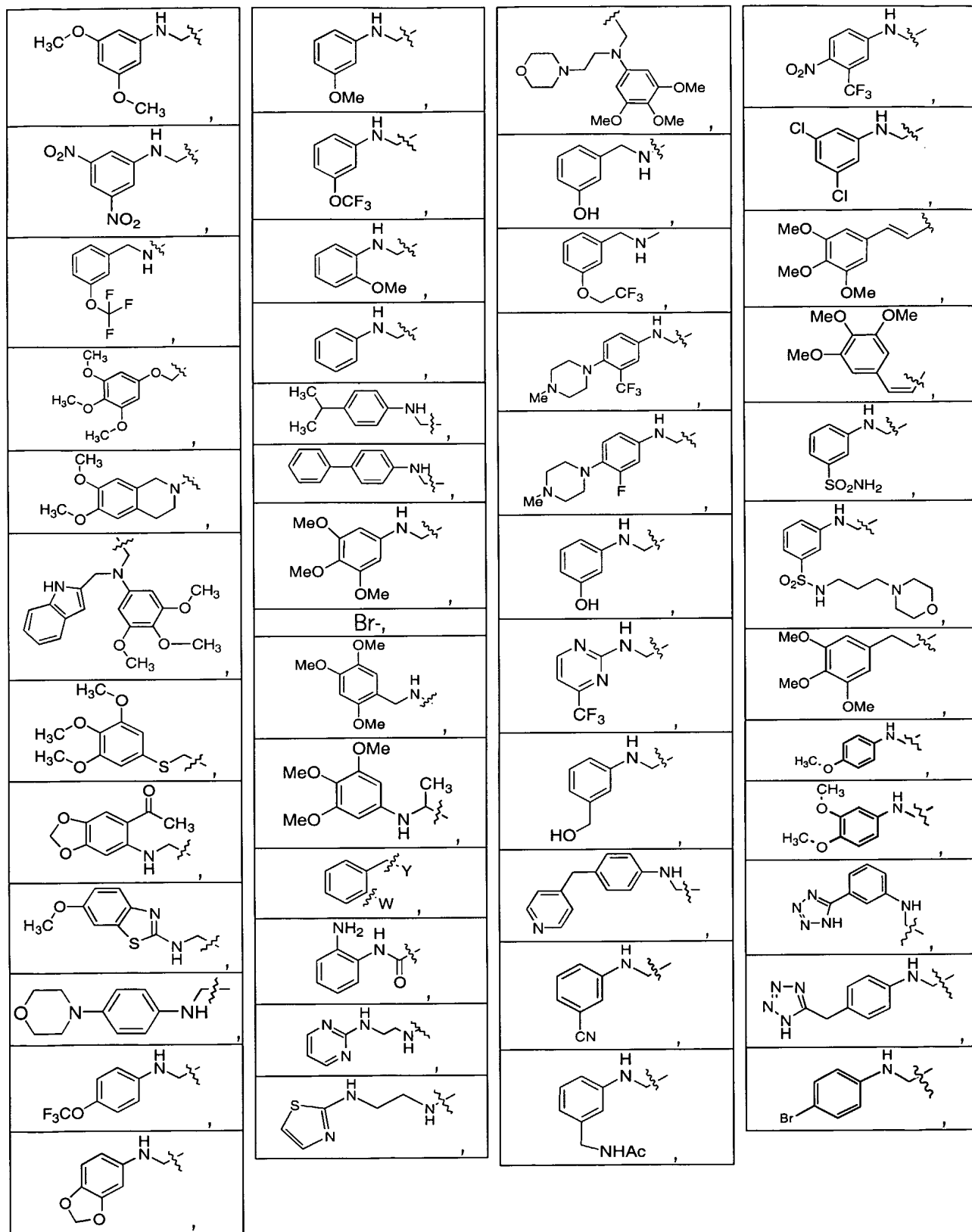
**[0075]** In some preferred embodiments of the compound according to paragraph [0073], V is an optionally substituted ring moiety selected from:

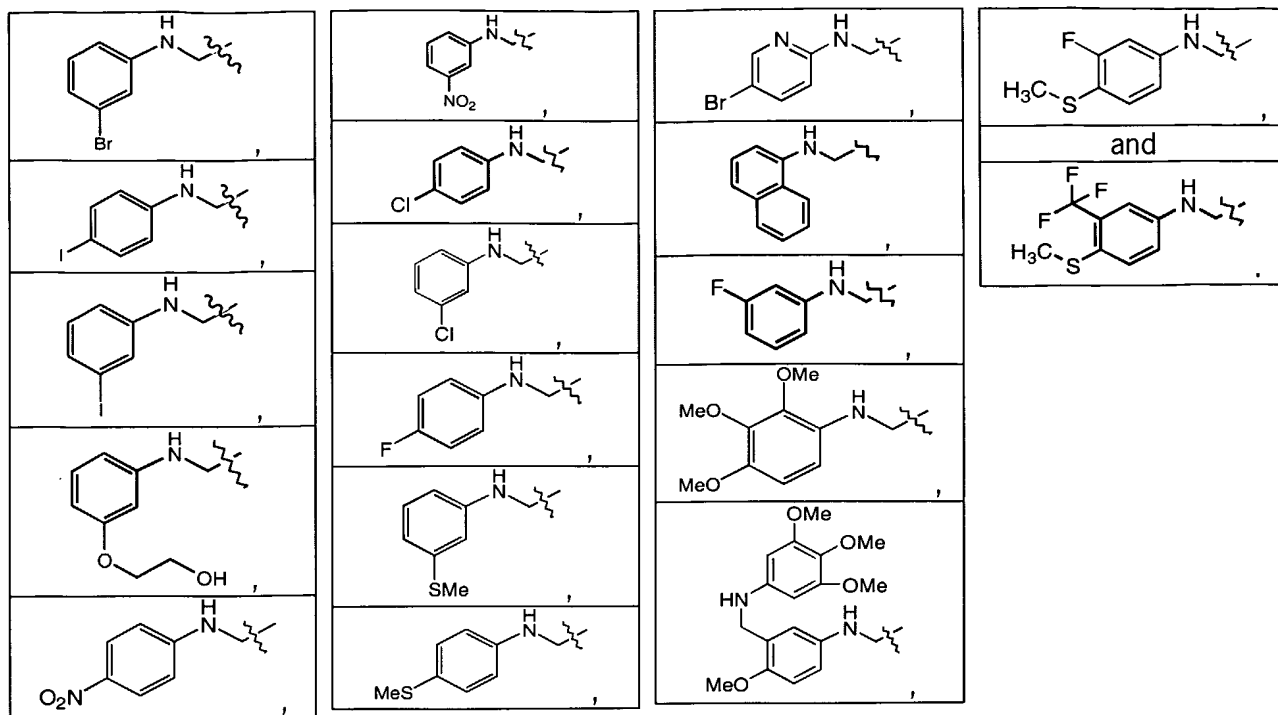


**[0076]** In another preferred embodiment of the compounds according to paragraph [0073], W is selected from:









**[0077]** In another preferred embodiment of the compounds according to paragraph [0073], the  $\mathcal{A}$  and  $\text{Ar}^a$  rings are not further substituted.

**[0078]** In a particularly preferred embodiment of the compounds according to paragraph [0073], the compounds of the invention are selected from the following, in which, unless expressly displayed otherwise,  $\text{Ar}^a$  is phenyl (and, preferably, the amide nitrogen and the amino nitrogen bound to  $\text{Ar}^a$  are *ortho* to each other):

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 481 |   | CH | CH | H              |
| 484 |   |    |    |                |
| 492 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 493 |   | CH | CH | H              |
| 494 |   | CH | CH | H              |
| 495 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 496 |   | CH | CH | H              |
| 497 |   | CH | CH | H              |
| 498 |   | CH | CH | H              |
| 499 |   | CH | CH | H              |
| 500 |   | CH | CH | H              |
| 501 |   | CH | CH | H              |
| 502 |   | CH | CH | H              |
| 503 |   | CH | CH | H              |
| 504 |   | CH | CH | H              |
| 505 |   | CH | CH | H              |
| 506 |   | CH | CH | H              |

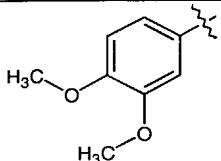
| Cpd | W | Y  | Z  | R <sup>6</sup>  |
|-----|---|----|----|-----------------|
| 507 |   | CH | CH | H               |
| 508 |   | CH | CH | H               |
| 509 |   | CH | CH | H               |
| 510 |   | CH | CH | H               |
| 511 |   | CH | CH | H               |
| 512 |   | CH | N  | H               |
| 516 |   | CH | CH | CH <sub>3</sub> |
| 517 |   | CH | CH | CH <sub>3</sub> |
| 518 |   | CH | CH | CH <sub>3</sub> |
| 519 |   | CH | CH | H               |
| 520 |   | CH | CH | H               |
| 521 |   | N  | CH | H               |
| 522 |   | N  | CH | H               |
| 523 |   | CH | CH | H               |

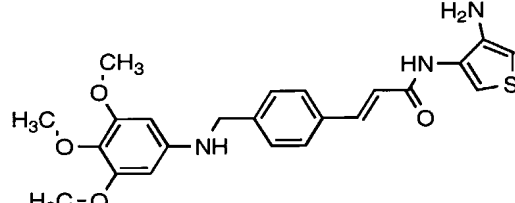
| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 524 |   | N  | CH | H              |
| 525 |   | N  | CH | H              |
| 526 |   | CH | CH | H              |
| 527 |   | CH | CH | H              |
| 528 |   | CH | CH | H              |
| 529 |   | CH | CH | H              |
| 530 |   | CH | CH | H              |
| 531 |   | CH | CH | H              |
| 532 |   | CH | CH | H              |
| 533 |   | CH | CH | H              |
| 534 |   | CH | CH | H              |
| 535 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 536 |   | CH | CH | H              |
| 537 |   | CH | CH | H              |
| 538 |   | CH | CH | H              |
| 539 |   | CH | CH | H              |
| 540 |   | CH | CH | H              |
| 541 |   | CH | CH | H              |
| 542 |   | CH | CH | H              |
| 543 |   | CH | CH | H              |
| 544 |   | CH | CH | H              |
| 545 |   | CH | CH | H              |
| 546 |   | CH | CH | H              |
| 547 |   | CH | CH | H              |

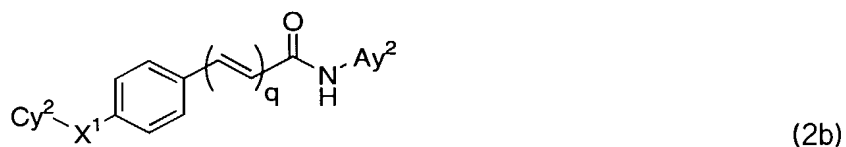
| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 548 |   | CH | CH | H              |
| 549 |   | CH | CH | H              |
| 550 |   | CH | CH | H              |
| 551 |   | CH | CH | H              |
| 552 |   | CH | CH | H              |
| 553 |   | CH | CH | H              |
| 554 |   | CH | CH | H              |
| 555 |   | CH | CH | H              |
| 556 |   | CH | CH | H              |
| 557 |   | CH | CH | H              |
| 558 |   | CH | CH | H              |
| 559 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 560 |   |    |    |                |
| 561 |   |    |    |                |
| 562 |   | CH | CH | H              |
| 563 |   | CH | CH | H              |
| 564 |   |    |    |                |
| 565 |   | CH | CH | H              |
| 566 |   | CH | CH | H              |
| 567 |   |    |    |                |
| 568 |   |    |    |                |

| Cpd | W   | Y  | Z | R <sup>6</sup> |
|-----|---|----|---|----------------|
| 569 |  | CH | N | H              |

| Cpd | W  | Y | Z | R <sup>6</sup> |
|-----|--|---|---|----------------|
| 570 |  |   |   |                |

**[0079]** In a preferred embodiment of the compounds according to paragraph [0057], the invention comprises compounds of the formula (2b):



and pharmaceutically acceptable salts thereof, wherein

Ay<sup>2</sup> is phenyl or thienyl, each substituted at the ortho position with -NH<sub>2</sub> or -OH and each further optionally substituted with one to three substituents independently selected from -NH<sub>2</sub>, -OH, and halo;

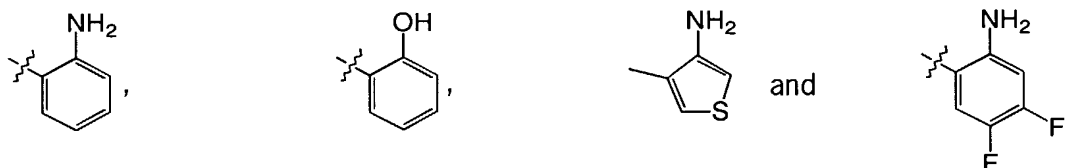
q is 0 or 1;

X<sup>1</sup> is selected from -CH<sub>2</sub>-, -NH-CH<sub>2</sub>-, and -S-CH<sub>2</sub>-;

Cy<sup>2</sup> is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH<sub>3</sub>-, CH<sub>3</sub>O-, phenyl optionally substituted with one to three CH<sub>3</sub>O-, morphylinyl, morphylinyl-C<sub>1</sub>-C<sub>3</sub>-alkoxy, cyano, and CH<sub>3</sub>C(O)NH-;

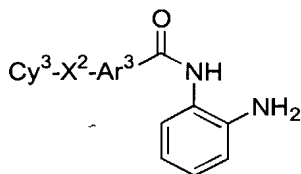
provided that when Cy<sup>2</sup> is naphthyl, X<sup>1</sup> is -CH<sub>2</sub>-, and q is 0 or 1, Ay<sup>2</sup> is not o-hydroxyphenyl.

**[0080]** Preferably in the compounds according to paragraph [0079], Ay<sup>2</sup> is selected from:



**[0081]** Preferably in the compounds according to paragraph [0079], Cy<sup>2</sup> is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinazolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH<sub>3</sub>O-. More preferably, Cy<sup>2</sup> is phenyl substituted with one to three CH<sub>3</sub>O-.

**[0082]** In a third embodiment, the novel inhibitors of histone deacetylase are represented by formula (3):



(3)

and pharmaceutical salts thereof, wherein

$Ar^3$  is arylene or heteroarylene, either of which optionally is substituted;

$Cy^3$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted;

provided that when  $Cy^3$  is a cyclic moiety having  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ , or  $-S(O)_2-$  in the ring, then  $Cy^3$  is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

$X^2$  is selected from the group consisting of a chemical bond,  $L^3$ ,  $W^1-L^3$ ,  $L^3-W^1$ ,  $W^1-L^3-W^1$ , and  $L^3-W^1-L^3$ , wherein

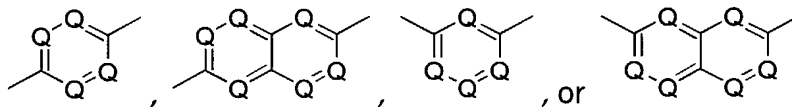
$W^1$ , at each occurrence, is S, O, or  $N(R^9)$ , where  $R^9$  is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

$L^3$  is  $C_1-C_4$  alkylene,  $C_2-C_4$  alkenylene, or  $C_2-C_4$  alkynylene;

provided that  $X^2$  does not comprise a  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ , or  $-S(O)_2-$  group;

and further provided that when  $Cy^3$  is pyridine, then  $X^2$  is  $L^3$ ,  $W^1-L^3$ , or  $L^3-W^1$ .

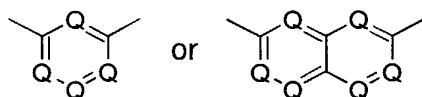
**[0083]** Preferably,  $Ar^3$  has the structure:



wherein Q, at each occurrence, is independently N or C, and C optionally is substituted.

**[0084]** Preferably in the compounds according to paragraph [0082],  $X^2$  is selected from the group consisting of  $L^3$ ,  $W^1-L^3$ ,  $L^3-W^1$ ,  $W^1-L^3-W^1$ , and  $L^3-W^1-L^3$ .

**[0085]** Preferably in the compounds according to paragraph [0082], when  $X^2$  is a chemical bond, then  $Ar^3$  is not



and  $Cy^3$  is not the radical of a substituted or unsubstituted diazepine or benzofuran.

**[0086]** In some embodiments of the compounds according to paragraph [0082], Q at each occurrence is  $C(R^8)$ , where  $R^8$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. In some other embodiments, from one to about three variables Q are nitrogen. In some preferred embodiments,  $Ar^3$  is selected from the group consisting of phenylene, pyridylene, thiazolylene, and quinolyne.

**[0087]** In some embodiments of the compounds according to paragraph [0082],  $X^2$  is a chemical bond. In other embodiments,  $X^2$  is a non-cyclic hydrocarbonyl. In some such embodiments,  $X^2$  is alkylene, preferably methylene or ethylene. In other such embodiments,  $X^2$  is alkenylene or alkynylene. In still other such embodiments, one carbon in the hydrocarbonyl chain is replaced with -NH- or -S-. In some preferred embodiments,  $X^2$  is  $W^1-L^3-W^1$  and  $W^1$  is -NH- or -N(CH<sub>3</sub>)-.

**[0088]** In some embodiments of the compounds according to paragraph [0082],  $Cy^3$  is cycloalkyl, preferably cyclohexyl. In other embodiments,  $Cy^3$  is aryl or heteroaryl, e.g., phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the cyclic moiety of  $Cy^3$  is fused to a benzene ring. In some embodiments,  $Cy^3$  has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl. Some other preferred substituents have the formula  $-K^1-N(H)(R^{10})$ , wherein

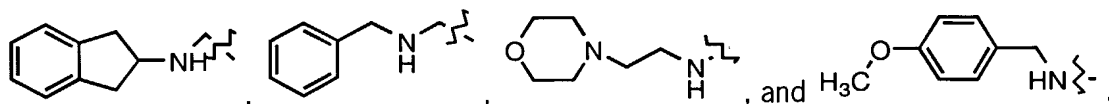
$K^1$  is a chemical bond or  $C_1-C_4$  alkylene;

$R^{10}$  is selected from the group consisting of  $Z'$  and  $-Ak^2-Z'$ , wherein

$Ak^2$  is  $C_1-C_4$  alkylene; and

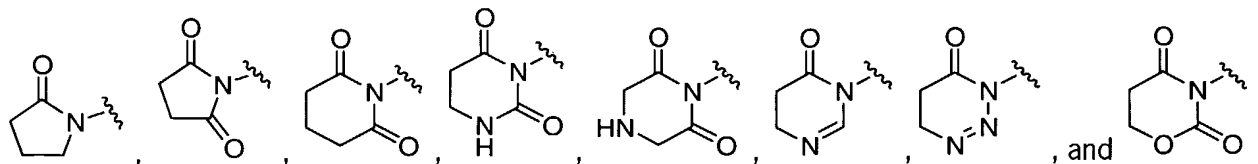
$Z'$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

**[0089]** Examples of such preferred substituents according to paragraph [0088] include





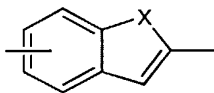
**[0090]** In some embodiments of the compounds according to paragraph [0082], Cy<sup>3</sup> is heterocyclyl, e.g.,



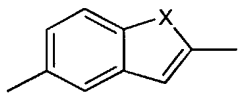
each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the heterocycle of Cy<sup>3</sup> is fused to a benzene ring.

**[0091]** Preferably in the compounds of paragraph [0082], when Ar<sup>4</sup> is quinoxalinylen, then X<sup>3</sup> is not -CH(OH)-.

**[0092]** In another preferred embodiment, Ar<sup>3</sup> is



wherein X is -CH<sub>2</sub>-, -NH-, O, or S. Preferably Ar<sup>3</sup> is



and X is S or O.

**[0093]** In a preferred embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0057] wherein

Ay<sup>2</sup> is ortho-aniliny;

q is 0; and

X<sup>1</sup> is M<sup>1</sup>-L<sup>2</sup>-M<sup>1</sup> or L<sup>2</sup>-M<sup>2</sup>-L<sup>2</sup>.

**[0094]** In a preferred embodiment of the compounds according to paragraph [0093], Ar<sup>2</sup> is aryl or heteroaryl; and Cy<sup>2</sup>-X<sup>1</sup>- is collectively selected from the group consisting of

- A<sub>1</sub>-L<sub>1</sub>-B<sub>1</sub>-, wherein A<sub>1</sub> is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L<sub>1</sub> is -(CH<sub>2</sub>)<sub>0-1</sub>NH(CH<sub>2</sub>)<sub>0-1</sub>-, -NHC(O)-, or -NHCH<sub>2</sub>-; and wherein B<sub>1</sub> is phenyl or a covalent bond;
- A<sub>2</sub>-L<sub>2</sub>-B<sub>2</sub>-, wherein A<sub>2</sub> is CH<sub>3</sub>(C=CH<sub>2</sub>)-, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L<sub>2</sub> is -C≡C-; and wherein B<sub>2</sub> is a covalent bond;

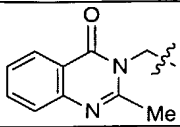
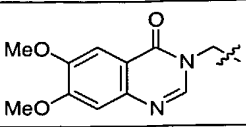
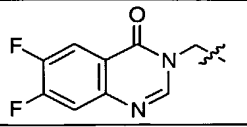
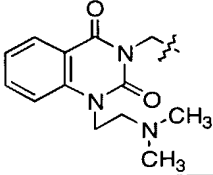
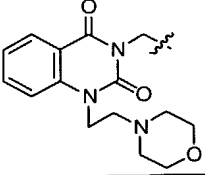
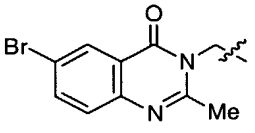
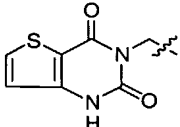
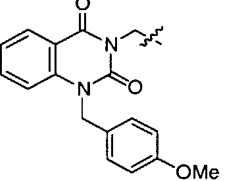
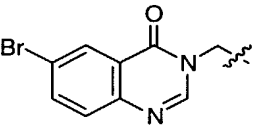
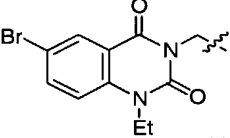
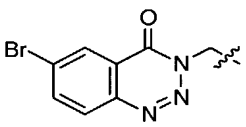
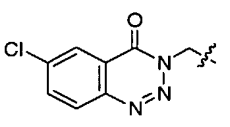
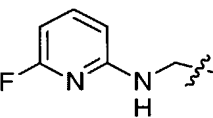
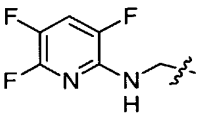
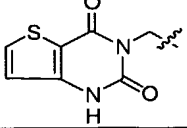
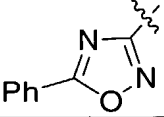
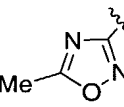
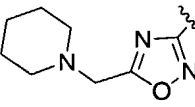
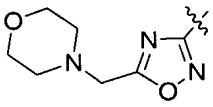
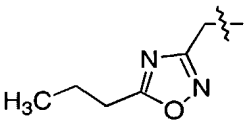
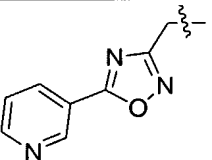
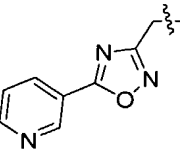
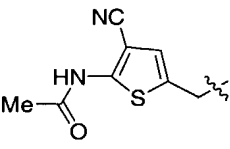
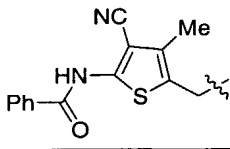
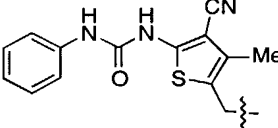
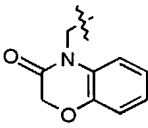
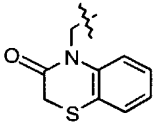
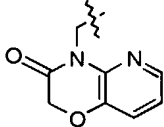
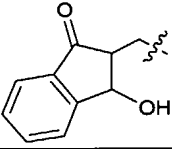
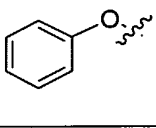
- c)  $A_3-L_3-B_3$ , wherein  $A_3$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_3$  is a covalent bond; and wherein  $B_3$  is  $-CH_2NH-$ ;
- d)  $A_4-L_4-B_4$ , wherein  $A_4$  is an optionally substituted aryl; wherein  $L_4$  is  $-NHCH_2-$ ; and wherein  $B_4$  is a thienyl group;
- e)  $A_5-L_5-B_5$ , wherein  $A_5$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_5$  is a covalent bond; and wherein  $B_5$  is  $-SCH_2-$ ;
- f) morpholinyl- $CH_2-$
- g) optionally substituted aryl;
- h)  $A_6-L_6-B_6$ , wherein  $A_6$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_6$  is a covalent bond; and wherein  $B_6$  is  $-NHCH_2-$ ;
- i)  $A_7-L_7-B_7$ , wherein  $A_7$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_7$  is a covalent bond; and wherein  $B_7$  is  $-CH_2-$ ;
- j) optionally substituted heteroaryl or optionally substituted heterocyclyl;
- k)  $A_8-L_8-B_8$ , wherein  $A_8$  is optionally substituted phenyl; wherein  $L_8$  is a covalent bond; and wherein  $B_8$  is  $-O-$ ;
- l)  $A_9-L_9-B_9$ , wherein  $A_9$  is an optionally substituted aryl; wherein  $L_9$  is a covalent bond; and wherein  $B_9$  is a furan group;
- m)  $A_{10}-L_{10}-B_{10}$ , wherein  $A_{10}$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{10}$  is  $-CH(CH_2CH_3)-$ ; and wherein  $B_{10}$  is  $-NHCH_2-$ ;
- n)  $A_{11}-L_{11}-B_{11}$ , wherein  $A_{11}$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{11}$  is a covalent bond; and wherein  $B_{11}$  is  $-OCH_2-$ ;
- o)  $A_{12}-L_{12}-B_{12}$ , wherein  $A_{12}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{12}$  is  $-NHC(O)-$ ; and wherein  $B_{12}$  is  $-N(\text{optionally substituted aryl})CH_2-$ ;
- p)  $A_{13}-L_{13}-B_{13}$ , wherein  $A_{12}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{13}$  is a covalent bond; and wherein  $B_{13}$  is  $-NHC(O)-$ ;

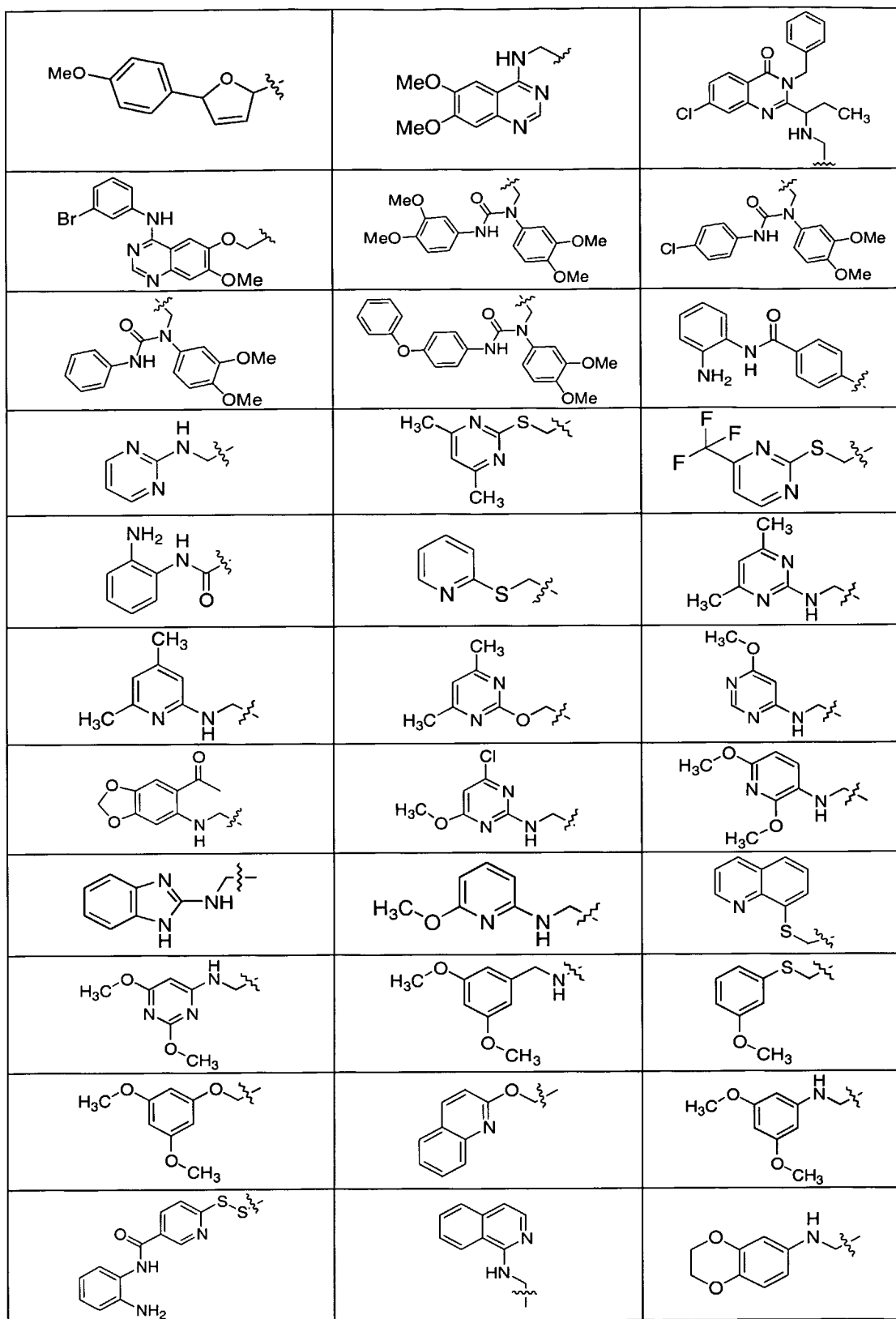
- q)  $A_{14}$ - $L_{14}$ - $B_{14}$ -, wherein  $A_{14}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{14}$  is  $-NHC(O)(\text{optionally substituted heteroaryl})$ ; and wherein  $B_{14}$  is  $-S-S-$ ;
- r)  $F_3CC(O)NH-$ ;
- s)  $A_{15}$ - $L_{15}$ - $B_{15}$ -, wherein  $A_{15}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{15}$  is  $-(CH_2)_{0,1}NH(\text{optionally substituted heteroaryl})$ ; and wherein  $B_{15}$  is  $-NHCH_2-$ ;
- t)  $A_{16}$ - $L_{16}$ - $B_{16}$ -, wherein  $A_{16}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{16}$  is a covalent bond; and wherein  $B_{16}$  is  $-N(\text{optionally substituted alkyl})CH_2-$ ; and
- u)  $A_{16}$ - $L_{16}$ - $B_{16}$ -, wherein  $A_{16}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{16}$  is a covalent bond; and wherein  $B_{16}$  is  $-(\text{optionally substituted aryl-CH}_2)_2N-$ .

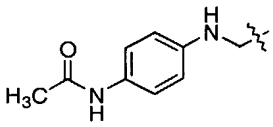
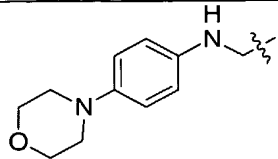
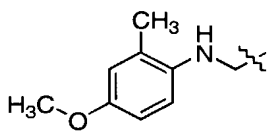
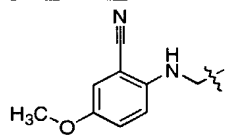
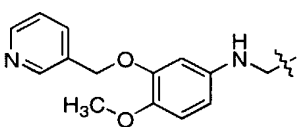
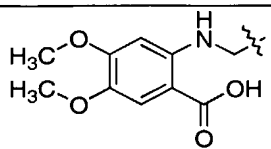
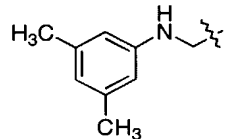
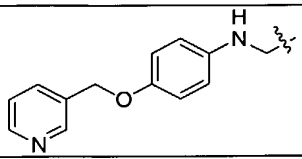
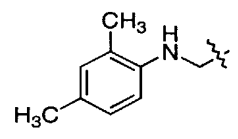
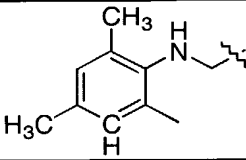
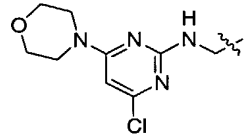
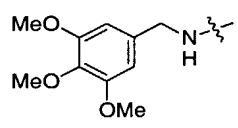
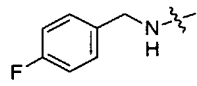
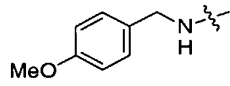
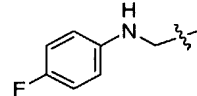
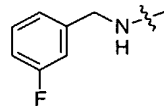
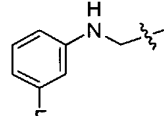
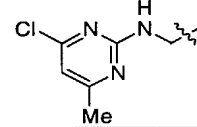
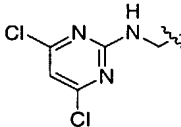
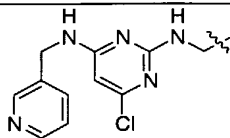
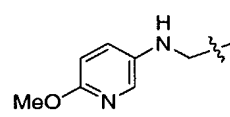
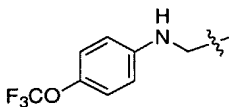
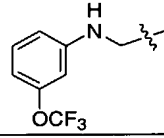
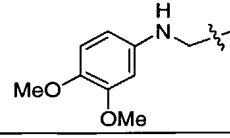
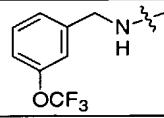
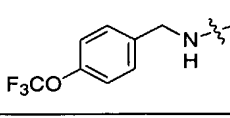
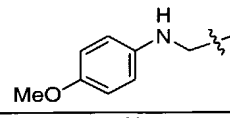
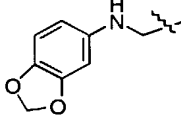
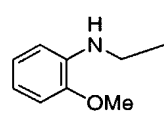
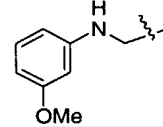
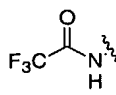
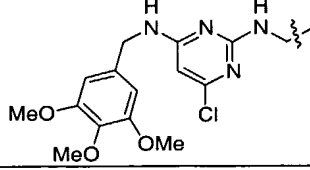
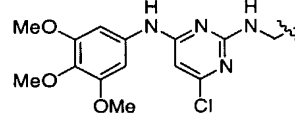
**[0095]** In another preferred embodiment of the compounds according to paragraph [0093],  $Cy^2-X^1-$  is collectively selected from the group consisting of

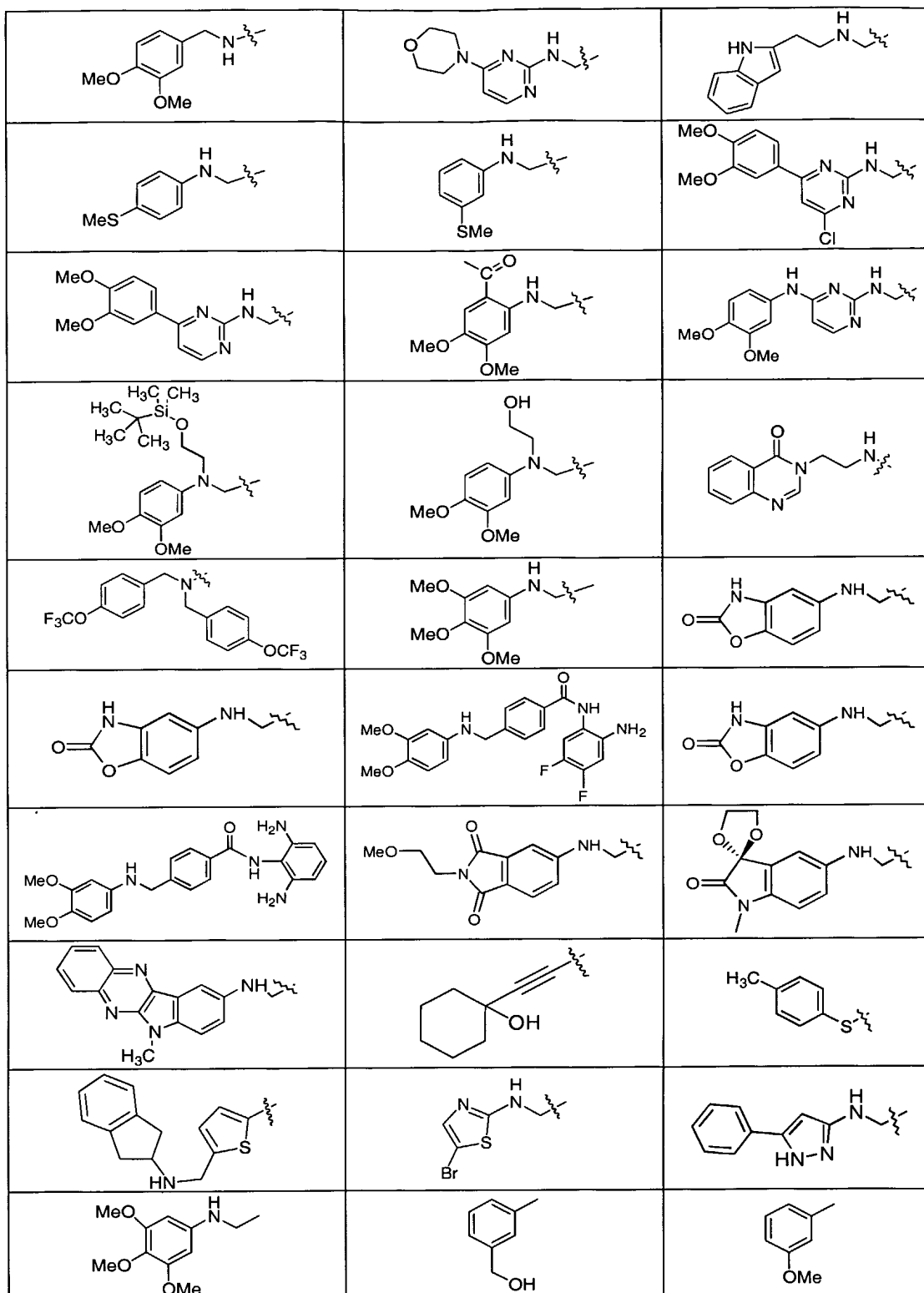
- a)  $D_1-E_1-F_1-$ , wherein  $D_1$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_1$  is  $-CH_2-$  or a covalent bond; and wherein  $B_1$  is a covalent bond;
- b)  $D_2-E_2-F_2-$ , wherein  $D_2$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_2$  is  $-NH(CH_2)_{0,2}-$ ; and wherein  $F_2$  is a covalent bond;
- c)  $D_3-E_3-F_3-$ , wherein  $D_3$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_3$  is  $-(CH_2)_{0,2}NH-$ ; and wherein  $F_3$  is a covalent bond;
- d)  $D_4-E_4-F_4-$ , wherein  $D_4$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_4$  is  $-S(CH_2)_{0,2}-$ ; and wherein  $F_4$  is a covalent bond;
- e)  $D_5-E_5-F_5-$ , wherein  $D_5$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_5$  is  $-(CH_2)_{0,2}S-$ ; and wherein  $F_5$  is a covalent bond; and



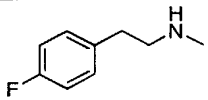
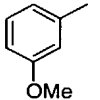
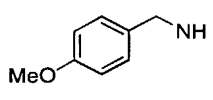
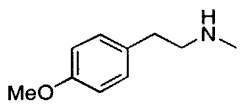
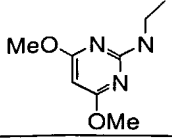
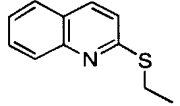
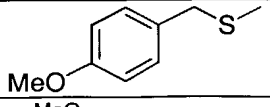
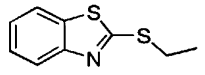
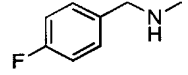
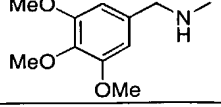
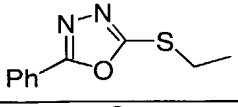
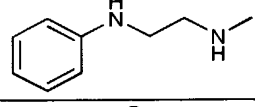
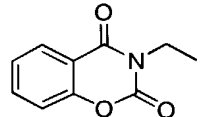
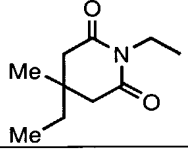
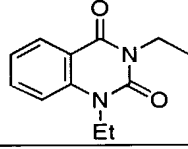
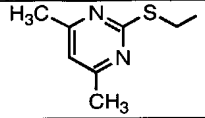
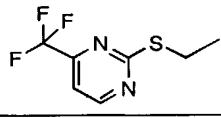
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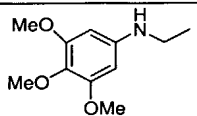
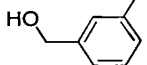
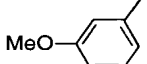
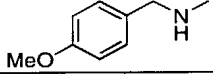
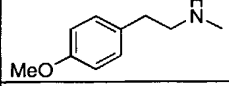
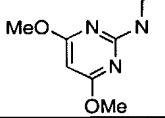
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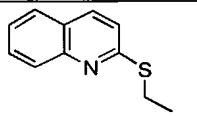
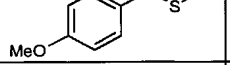
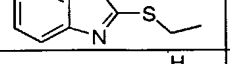
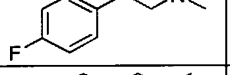
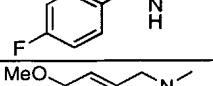
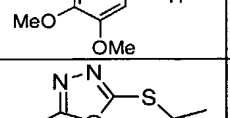
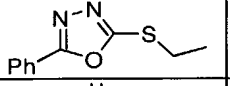
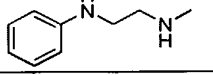


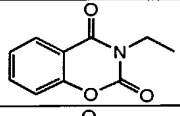
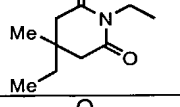
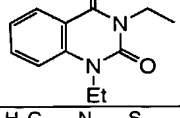
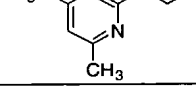
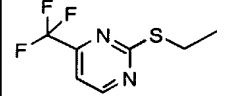


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|  |  |  |
|  | and   |  |

[0097] In a preferred embodiment of the compounds according to paragraph [0096], the compounds comprise those wherein Y, Z and W are as defined below:

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 164 |  | CH | CH |
| 165 |  | N  | CH |
| 166 |  | CH | CH |
| 167 |  | CH | N  |
| 168 |  | CH | N  |
| 169 |  | CH | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 170 |  | CH | CH |
| 171 |  | N  | CH |
| 172 |  | CH | CH |
| 174 |  | CH | N  |
| 175 |  | CH | N  |
| 176 |  | CH | N  |
| 177 |  | CH | CH |
| 178 |  | N  | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 179 |  | CH | CH |
| 180 |  | CH | CH |
| 181 |  | CH | CH |
| 182 |  | CH | CH |
| and |   |    |    |
| 183 |  | CH | CH |

[0098] In another preferred embodiment of the compounds according to paragraph [0096], the compounds comprise those wherein Y, Z and W are as defined below:

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 187 |   | CH | CH |
| 188 |   | CH | CH |
| 189 |   | CH | CH |
| 190 |   | CH | CH |
| 193 |   | CH | CH |
| 194 |   | CH | CH |
| 195 |   | CH | CH |
| 196 |   | CH | CH |
| 320 |   | CH | CH |
| 321 |   | CH | CH |
| 322 |   | CH | CH |
| 323 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 325 |   | CH | CH |
| 326 |   | CH | CH |
| 327 |   | CH | CH |
| 328 |   | CH | CH |
| 329 |   | CH | CH |
| 330 |   | CH | CH |
| 331 |   | CH | CH |
| 332 |   | CH | CH |
| 333 |   | CH | CH |
| 334 |   | CH | CH |
| 335 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 336 |   | CH | CH |
| 337 |   | CH | CH |
| 338 |   | CH | CH |
| 339 |   | CH | CH |
| 340 |   | CH | CH |
| 341 |   | CH | CH |
| 342 |   | CH | CH |
| 343 |   | CH | CH |
| 344 |   | CH | CH |
| 345 |   | CH | CH |
| 346 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 347 |   | CH | CH |
| 348 |   | CH | CH |
| 349 |   | CH | CH |
| 350 |   | CH | CH |
| 351 |   | CH | CH |
| 352 |   | CH | CH |
| 353 |   | CH | CH |
| 354 |   | CH | CH |
| 355 |   | CH | CH |
| 356 |   | CH | CH |
| 357 |   | CH | CH |
| 358 |   | CH | CH |
| 359 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 360 |   | CH | CH |
| 361 |   | CH | CH |
| 362 |   | CH | CH |
| 363 |   | CH | CH |
| 364 |   | CH | CH |
| 365 |   | CH | CH |
| 366 |   | CH | CH |
| 367 |   | CH | CH |
| 368 |   | CH | CH |
| 369 |   | CH | CH |
| 370 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 371 |   | CH | CH |
| 372 |   | CH | CH |
| 373 |   | CH | CH |
| 374 |   | CH | CH |
| 375 |   | CH | CH |
| 377 |   | CH | CH |
| 378 |   | CH | CH |
| 379 |   | CH | CH |
| 380 |   | N  | CH |
| 381 |   | CH | CH |
| 382 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 383 |   | CH | CH |
| 384 |   | CH | CH |
| 385 |   | CH | CH |
| 386 |   | CH | CH |
| 387 |   | CH | CH |
| 388 |   | CH | CH |
| 389 |   | CH | CH |
| 390 |   | CH | CH |
| 391 |   | CH | CH |
| 392 |   | CH | CH |
| 393 |   | CH | CH |
| 394 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 395 |   | CH | CH |
| 396 |   | CH | CH |
| 397 |   | CH | CH |
| 398 |   | CH | N  |
| 399 |   | CH | CH |
| 400 |   | CH | CH |
| 401 |   | CH | CH |
| 402 |   | CH | CH |
| 403 |   | CH | CH |
| 404 |   | CH | CH |
| 405 |   | CH | CH |
| 406 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 407 |   | CH | CH |
| 408 |   | CH | CH |
| 409 |   | CH | CH |
| 410 |   | CH | CH |
| 411 |   | CH | CH |
| 412 |   | CH | CH |
| 413 |   | CH | CH |
| 414 |   | CH | CH |
| 415 |   | CH | CH |
| 416 |   | CH | CH |
| 417 |   | CH | CH |
| 418 |   | CH | CH |

| Cpd  | W | Y  | Z  |
|------|---|----|----|
| 419  |   | CH | CH |
| 420  |   | CH | CH |
| 421  |   | CH | CH |
| 422  |   | CH | CH |
| 423  |   | CH | CH |
| 424b |   | CH | CH |
| 425  |   | CH | CH |
| 426  |   | CH | CH |
| 427  |   | CH | CH |
| 428  |   | CH | CH |
| 429  |   | CH | CH |
| 430  |   | CH | CH |

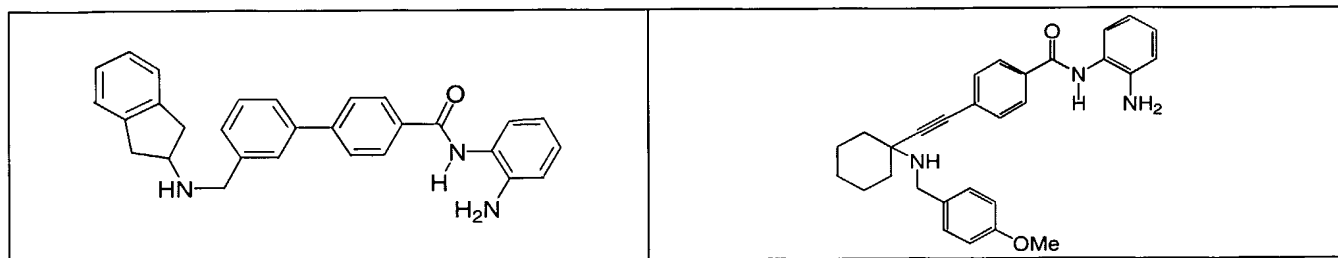
| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 431 |   | CH | CH |
| 432 |   | CH | CH |
| 433 |   | CH | CH |
| 434 |   | CH | CH |
| 435 |   | CH | CH |
| 436 |   | CH | CH |
| 437 |   | CH | CH |
| 438 |   | CH | CH |
| 439 |   | CH | CH |
| 440 |   | CH | CH |
| 441 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 442 |   | CH | CH |
| 443 |   | CH | CH |
| 444 |   | CH | CH |
| 445 |   | CH | N  |
| 446 |   | CH | N  |
| 447 |   | CH | CH |
| 448 |   | CH | CH |
| 449 |   | CH | CH |
| 450 |   | CH | CH |
| 451 |   | CH | CH |
| 452 |   | CH | CH |
| 453 |   |    |    |

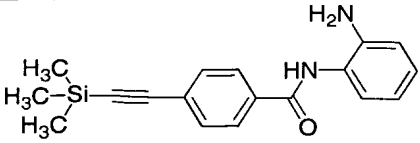
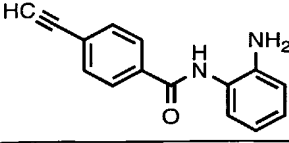
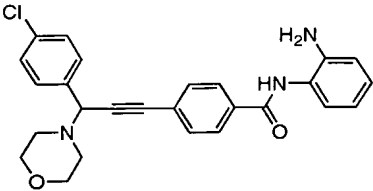
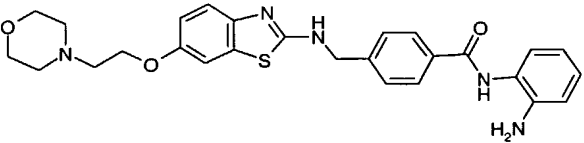
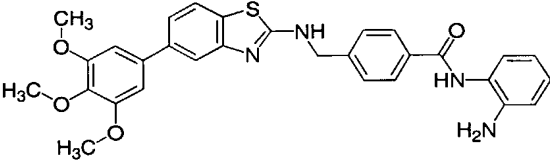
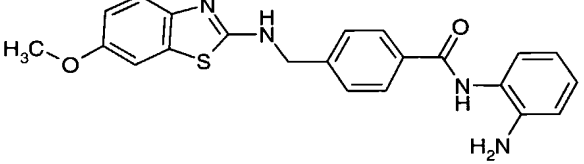
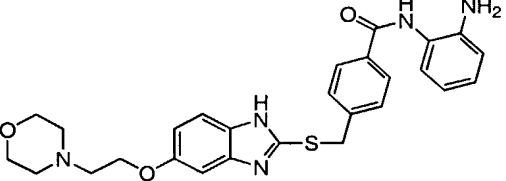
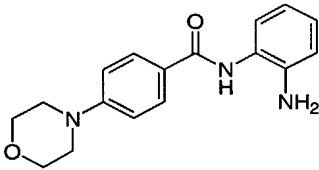
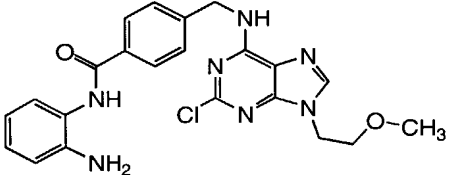
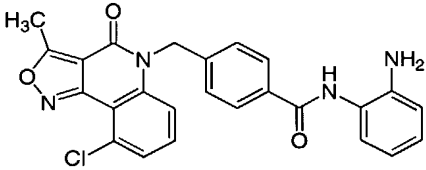
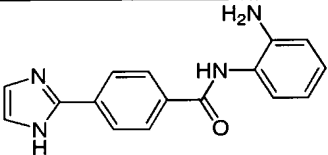
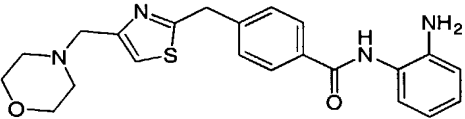
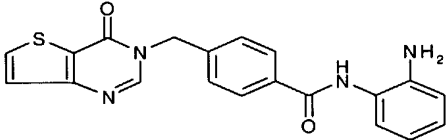
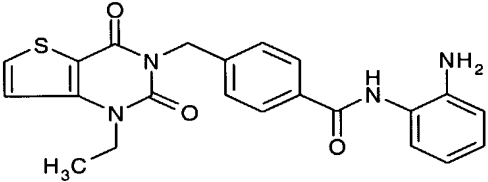
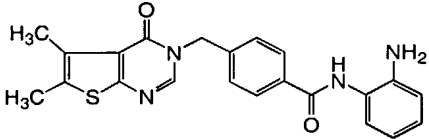
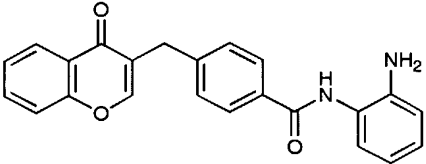
| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 454 |   |    |    |
| 455 |   | CH | CH |
| 456 |   | CH | CH |
| 457 |   |    |    |
| 458 |   | CH | CH |
| 459 |   | CH | CH |
| 460 |   | CH | N  |
| 461 |   | CH | CH |

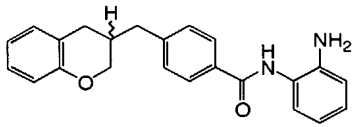
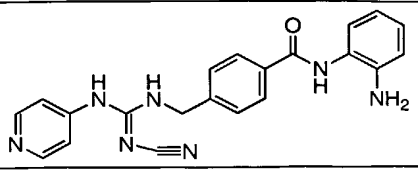
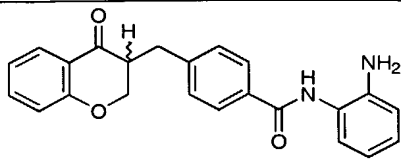
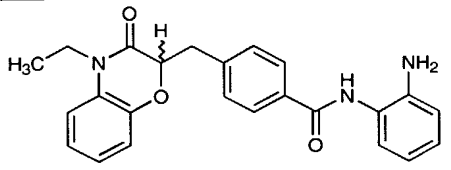
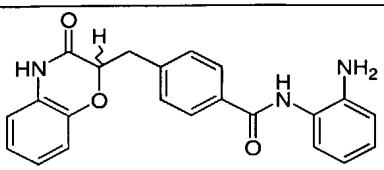
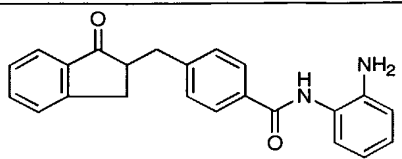
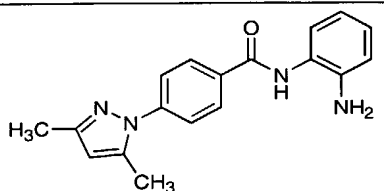
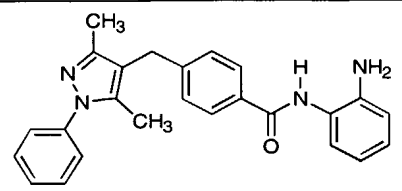
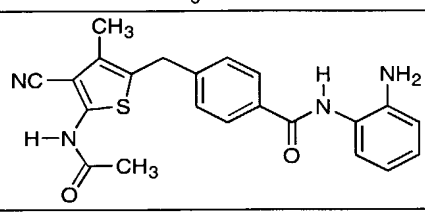
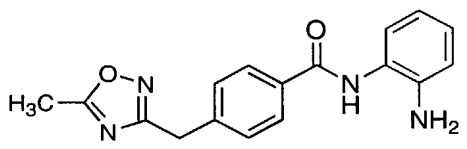
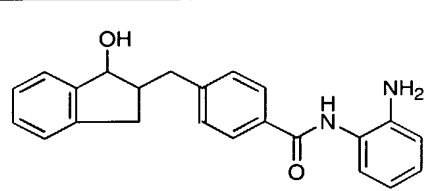
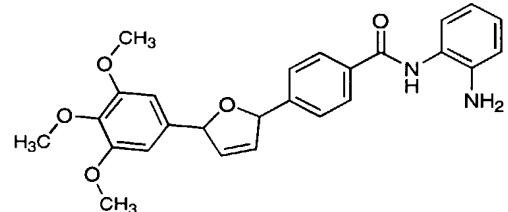
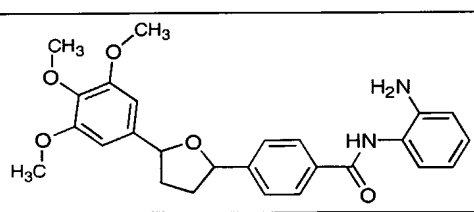
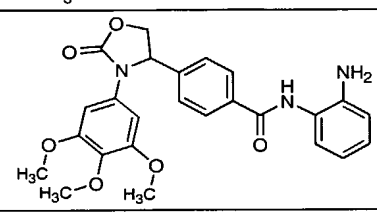
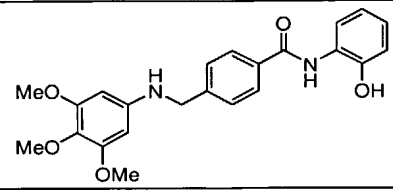
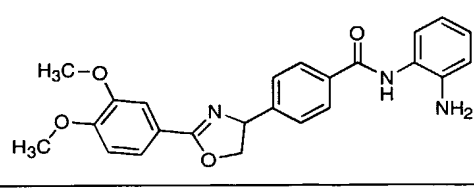
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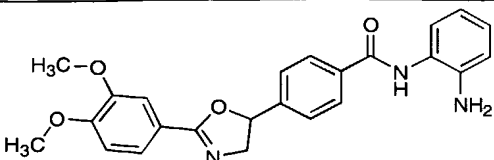
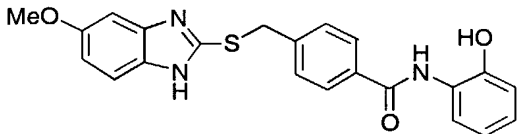
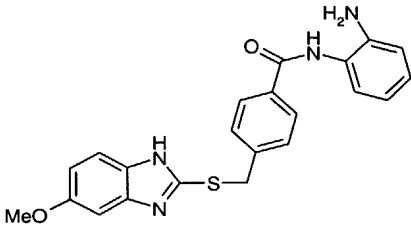
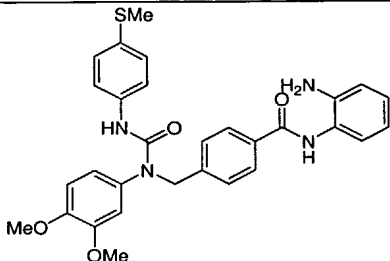
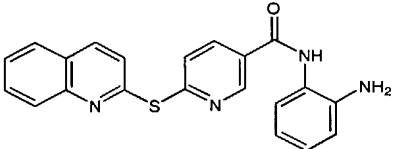
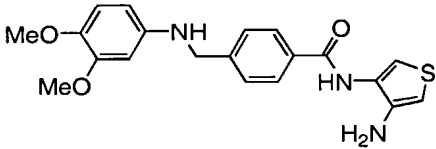
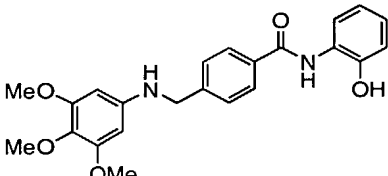
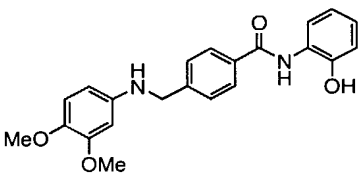
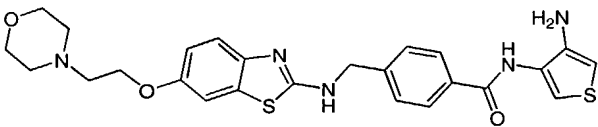
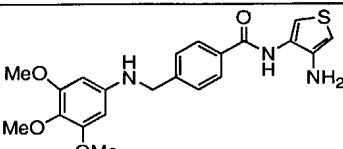
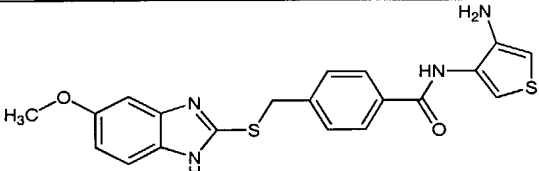
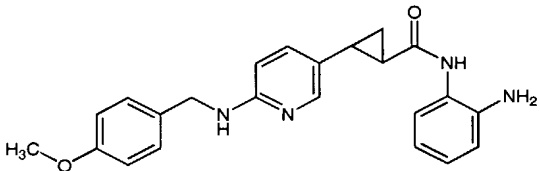
**[0099]** In yet another a preferred embodiment, the novel histone deacetylase inhibitors of the invention are selected from the group consisting of the following and their pharmaceutically acceptable salts:





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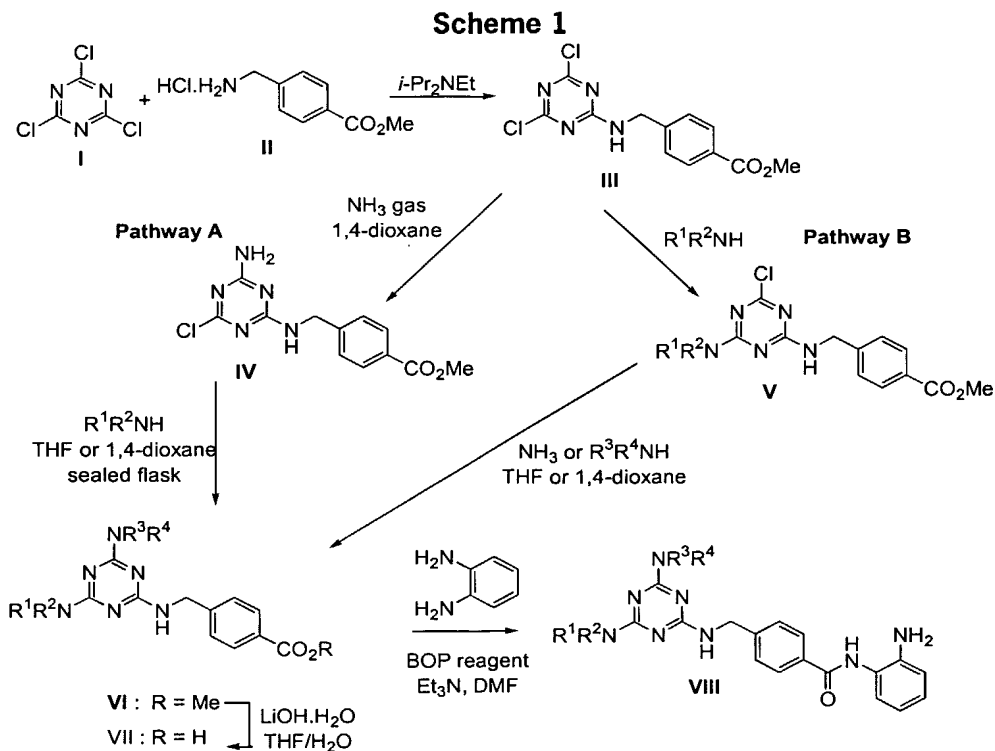
[0100] In another preferred embodiment, the compounds are selected from those listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f.

### Synthesis

[0101] Compounds of formula (1), wherein  $Y^1$  is  $-N(R^1)(R^2)$ , preferably may be prepared according to the synthetic route depicted in Scheme 1. Thus, trichlorotriazine **I** reacts with amine **II** in the presence of diisopropylethylamine to produce dichloroaminotriazine **III**. The amine  $R^1R^2NH$  is added to dichloroaminotriazine **III** to produce diaminochlorotriazine **V**. Treatment of **V** with ammonia or  $R^3R^4NH$  in tetrahydrofuran (THF) or 1,4 dioxane affords triaminotriazine **VI**.

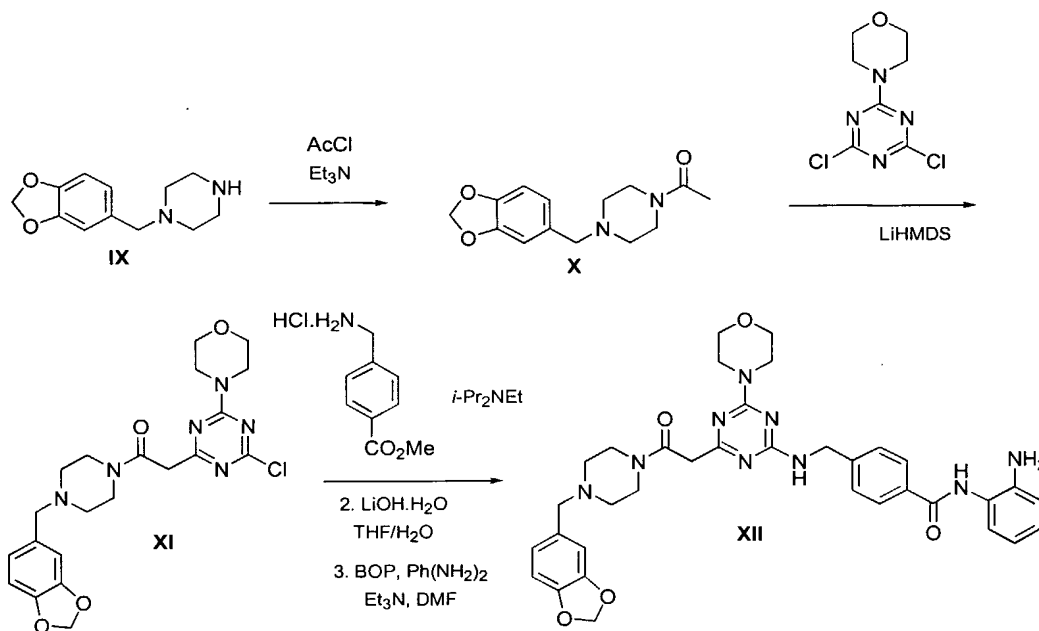
[0102] Alternatively, dichloroaminotriazine **III** may be reacted with ammonia gas in 1,4 dioxane to produce diaminochlorotriazine **IV**. Treatment of **IV** with  $R^1R^2NH$  in THF or 1,4 dioxane in a sealed flask then affords triaminotriazine **VI**.

[0103] Hydrolysis of the ester moiety in **VI** is effected by treatment with a hydroxide base, such as lithium hydroxide, to afford the corresponding acid **VII**. Treatment of the acid **VII** with 1,2-phenylenediamine in the presence of BOP reagent, triethylamine, and dimethylformamide (DMF) yields the aniliny amide **VIII**.



[0104] Compounds of formula (1), wherein  $Y^1$  is  $-CH_2-C(O)-N(R^1)(R^2)$ , preferably may be prepared as outlined in Scheme 2. Thus, piperazine **IX** is treated with acetyl chloride and triethylamine to produce amide **X**. Reaction of **X** with dichloromorpholytriazine and lithium hexamethyldisiloxane affords compound **XI**. The chloride of **XI** is converted to the aniliny amide of **XII** as described above with respect to Scheme 1: treatment with the amine and diisopropylethylamine; followed by lithium hydroxide; followed by BOP reagent, phenylenediamine, triethylamine, and DMF.

Scheme 2

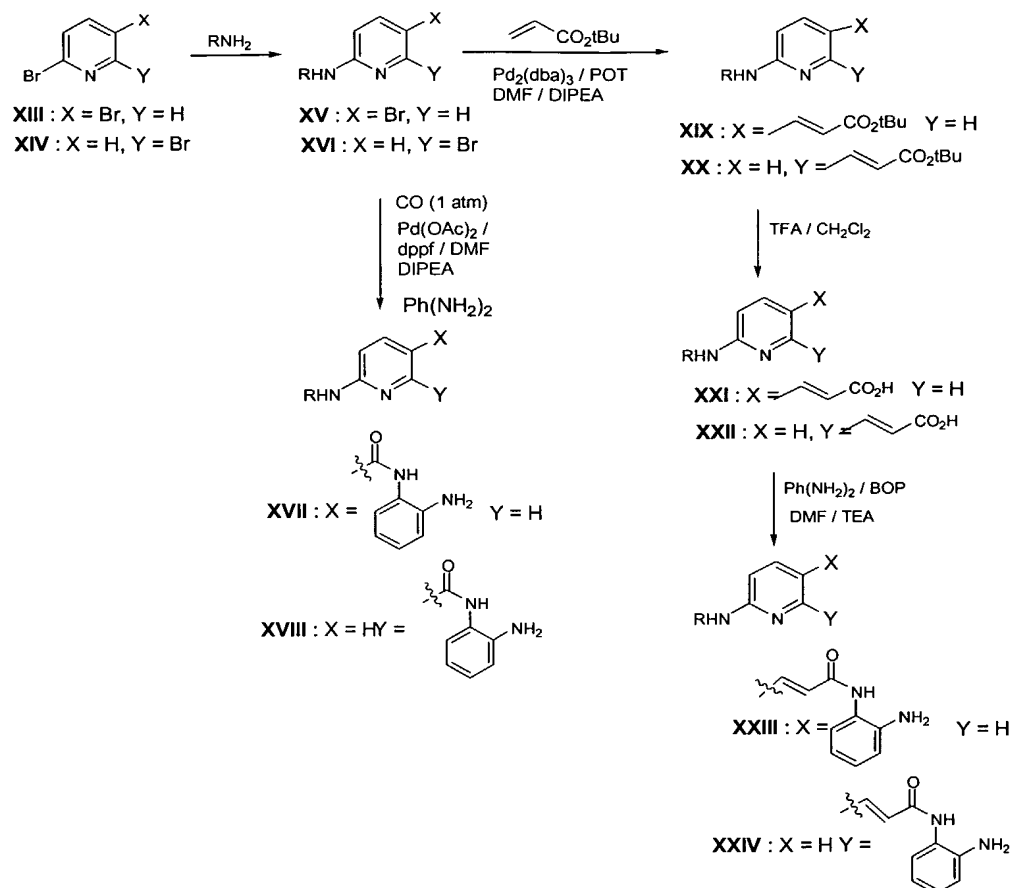


[0105] Compounds of formula (2), wherein  $Ar^2$  is pyridylene and  $X^1$  comprises  $-N(R^7)$ , compounds of formula (3), wherein  $Ar^3$  is pyridylene and  $X^2$  comprises  $-N(R^9)$ , and compounds of formula (4), wherein  $Ar^4$  is pyridylene and  $X^3$  comprises  $-N(R^{11})$ , preferably may be prepared according to the procedures illustrated in Scheme 3. Dibromopyridine **XIII** or **XIV** is treated with amine  $RNH_2$  to produce aminobromopyridine **XV** or **XVI**, respectively. Treatment of **XV** or **XVI** with diacetoxypalladium, diphenylphosphinoferrocene, DMF, diisopropylethylamine, and phenylenediamine under carbon monoxide yields aniliny amide **XVII** or **XVIII**, respectively.

[0106] Treatment of **XV** or **XVI** with tert-butylacrylate, diisopropylethylamine, dibenzylacetone palladium, and tri-*o*-tolylphosphine (POT) in DMF under nitrogen affords compounds **XIX** and **XX**, respectively. The ester moiety of **XIX** or **XX** is hydrolyzed to produce the corresponding acid moiety in **XXI** or **XXII**, respectively, by reaction with trifluoroacetic acid in dichloromethane. Treatment of

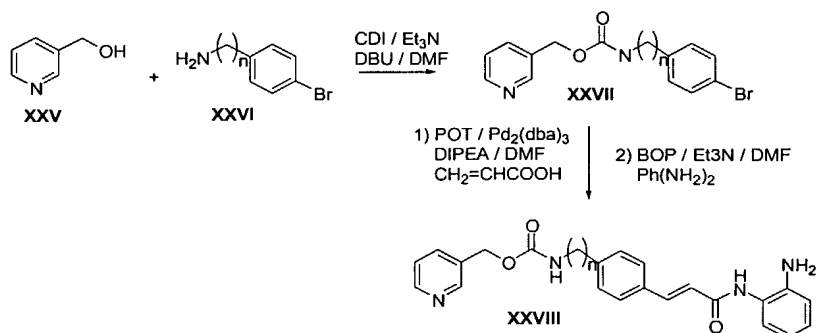
the acid **XXI** or **XXII** with phenylenediamine, BOP, and triethylamine affords the anilinyI amide **XXIII** or **XXIV**, respectively.

Scheme 3



**[0107]** Compounds of formula (2), wherein  $X^1$  comprises  $-\text{O}-\text{C}(\text{O})-\text{NH}-$ , preferably may be prepared according to the synthetic route depicted in Scheme 4. Thus, carbinol **XXV** is added to bromobenzylamine **XXVI** with carbonyldiimidazole (CDI), triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to produce compound **XXVII**. The remaining synthetic steps in the production of anilinyI amide **XXVIII** are as described above for Scheme 3.

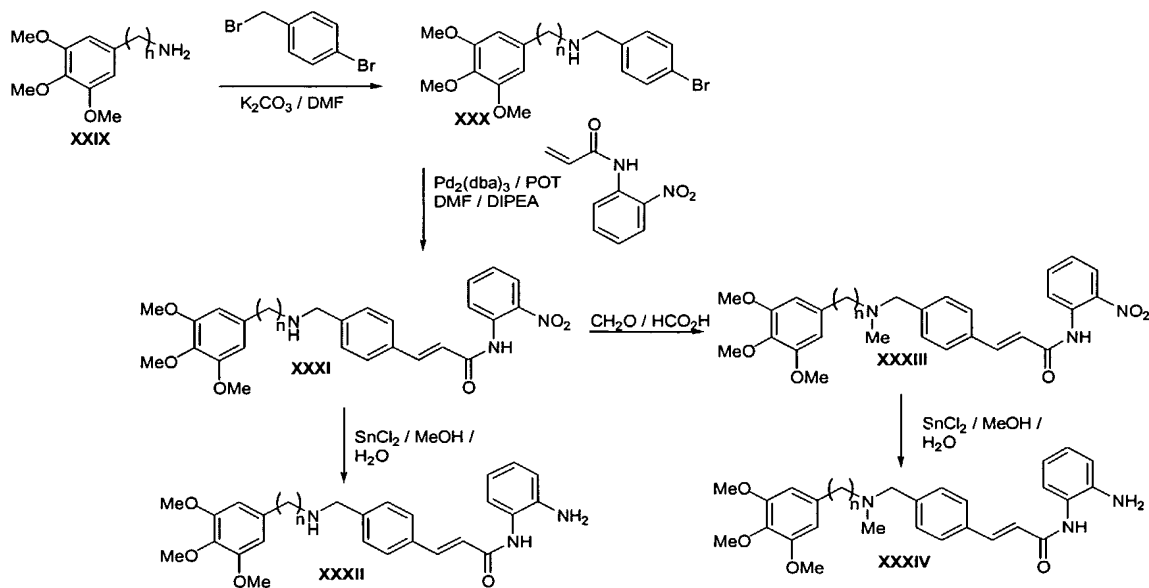
## Scheme 4



**[0108]** Compounds of formula (2), wherein  $X^1$  comprises  $-N(R^7)-$ , preferably may be prepared as outlined in Scheme 5. Amine XXIX is reacted with p-bromobenzylbromide in the presence of potassium carbonate in DMF to produce bromobenzylamine XXX. Treatment of XXX with nitroacrylanilide, dibenzylacetone palladium, POT, and diisopropylethylamine in DMF affords nitroanilide XXXI. Nitroanilide XXXI is converted to the corresponding anilinyll amide XXXII by treatment with stannous chloride in methanol and water.

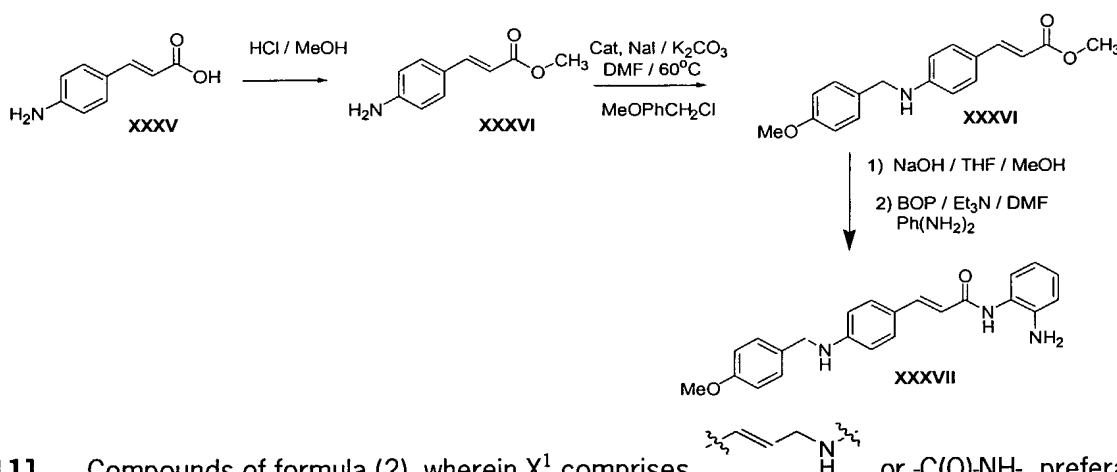
**[0109]** Treatment of amine XXXI in formic acid with paraformaldehyde provides methylamine XXXIII. The nitroanilide moiety in XXXIII is then converted to the corresponding anilinyll amide moiety in XXXIV by treatment with stannous chloride in methanol and water.

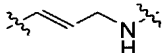
## Scheme 5



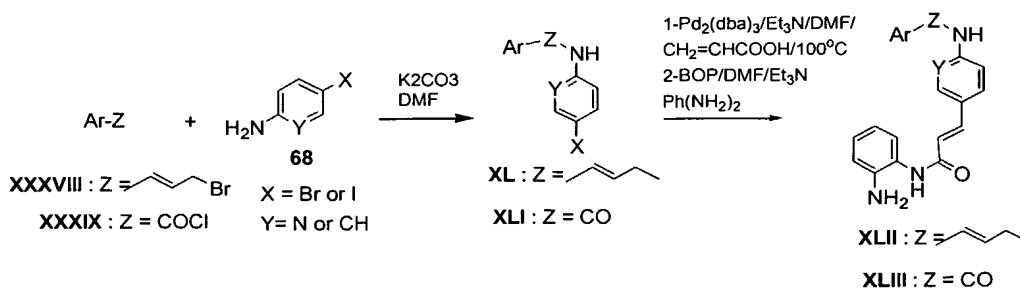
**[0110]** Alternatively, compounds of formula (2), wherein  $X^1$  comprises  $-N(R^7)-$ , may be prepared according to the synthetic route depicted in Scheme 6. Carboxylic acid **XXXV** in methanol is treated with hydrochloric acid to produce ester **XXXVI**. Conversion of the primary amine moiety in **XXXVI** to the secondary amine moiety in **XXXVI** is effected by treatment with a catalyst such as triethylamine, methoxybenzylchloride, sodium iodide, and potassium carbonate in DMF at 60 °C. Ester **XXXVI** is converted to anilinyll amide **XXXVII** by treatment with sodium hydroxide, THF, and methanol, followed by BOP, triethylamine, and phenylenediamine in DMF, as described above for Scheme 3.

Scheme 6



**[0111]** Compounds of formula (2), wherein  $X^1$  comprises  or  $-C(O)-NH-$ , preferably may be prepared according to the procedures illustrated in Scheme 7. Addition of amine **68** to haloaryl compound **XXXVIII** or **XXXIX** and potassium carbonate in DMF provides arylamine **XL** or **XLI**, respectively. Anilinyll amide **XLII** or **XLIII** is then prepared using procedures analogous to those set forth in Schemes 3-6 above.

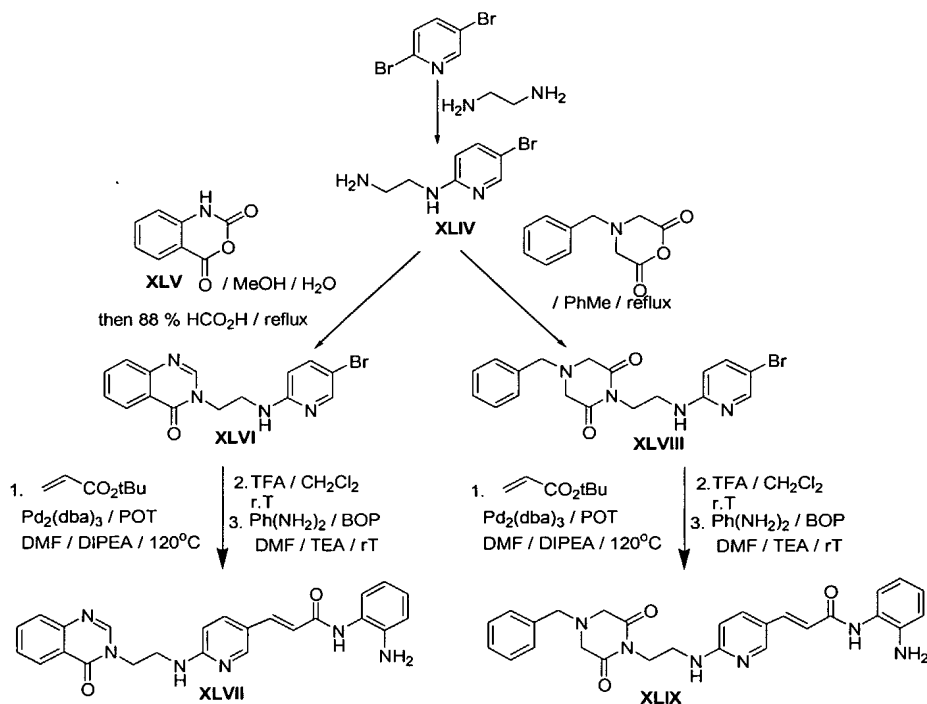
Scheme 7





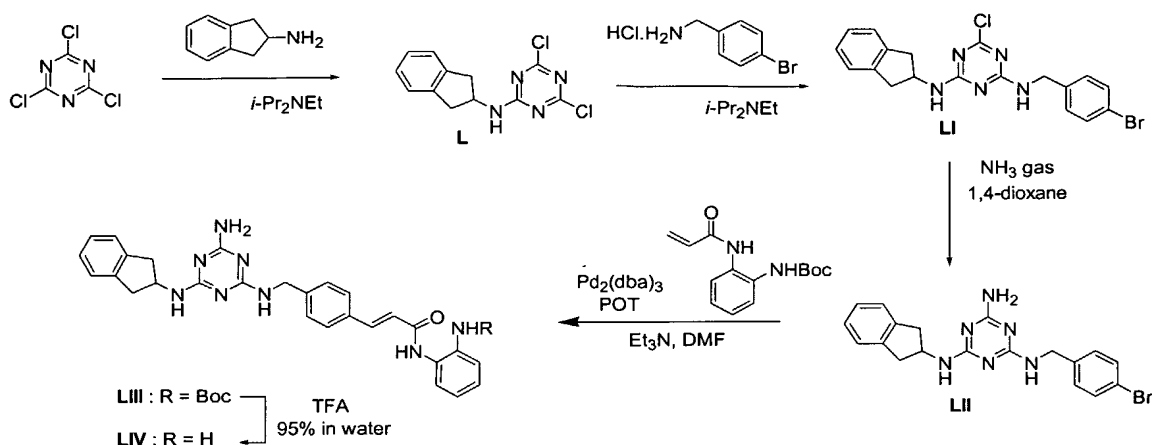
**[0112]** Compounds such as **XLVII** and **XLIX** preferably may be prepared as outlined in Scheme 8. Dibromopyridine is combined with diaminoethane to produce amine **XLIV**. Treatment of amine **XLIV** with isatoic anhydride **LV** in methanol and water, followed by refluxing in formic acid affords compound **XLVI**. Treatment of amine **XLIV** with the reaction products of benzylaminodiacetic acid and acetic anhydride provides compound **XLVIII**. Bromopyridylamines **XLVI** and **XLVIII** are then converted to the corresponding diene anilinyllamides **XLVII** and **XLIX**, respectively, by procedures analogous to those set forth in Schemes 3-7 above.

Scheme 8



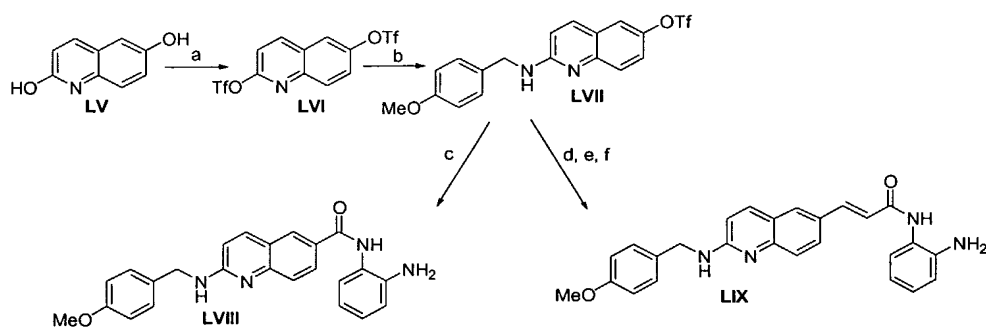
**[0113]** Compounds such as **LIV** preferably may be prepared according to the synthetic route depicted in Scheme 9. Trichlorotriazine is treated with aminoindan and diisopropylethylamine to produce dichloroaminotriazine **L**. Treatment with bromobenzylamine and diisopropylethylamine affords diaminochlorotriazine **LI**. Addition of ammonia gas and dioxane provides triaminotriazine **LII**. Treatment with protected acrylanilide, triethylamine, POT, and dibenzylacetone palladium then yields diene anilinyllamide **LIII**, which is deprotected with trifluoroacetic acid to provide the final product **LIV**.

## Scheme 9



**[0114]** Compounds of formula (2), wherein Ar<sup>2</sup> is quinolylene and X<sup>1</sup> comprises -N(R<sup>7</sup>)-, compounds of formula (3), wherein Ar<sup>3</sup> is quinolylene and X<sup>2</sup> comprises -N(R<sup>9</sup>)-, and compounds of formula (4), wherein Ar<sup>4</sup> is quinolylene and X<sup>3</sup> comprises -N(R<sup>11</sup>)-, preferably may be prepared according to the procedures illustrated in Scheme 10. Dihydroxyquinoline LV with dimethylaminopyridine (DMAP) in pyridine is treated with trifluoromethanesulfonyl anhydride to provide bis(trifluoromethanesulfonyloxy)-quinoline LVI. Treatment of LVI with p-methoxybenzylamine affords aminoquinoline LVII. Anilinyll amides LVIII and LIX are then prepared using procedures analogous to those described for Schemes 1-9 above.

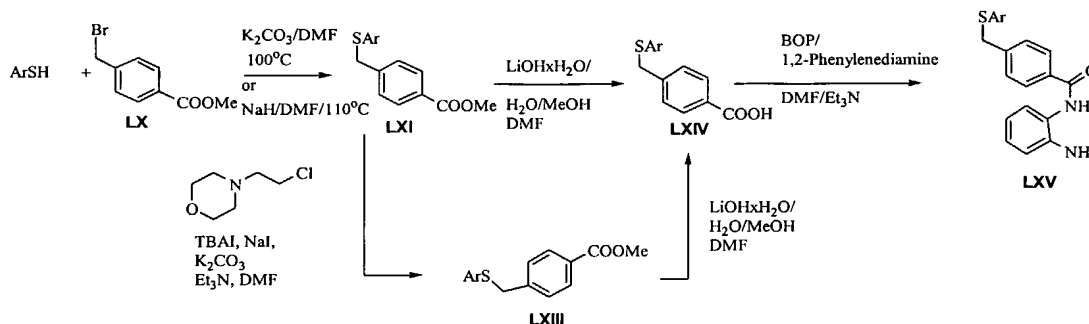
## Scheme 10



- a. Tf<sub>2</sub>O / Py / DMAP / 0 C
- b. p-methoxybenzylamine / 120 C
- c. 1,2-phenylenediamine / CO (40 psi) / Pd(OAc)<sub>2</sub> / dppf / DMF / DIPEA / 70 C
- d. t Butylacrylate / Pd<sub>2</sub>(dba)<sub>3</sub> / POT / DMF / DIPEA / 120 C
- e. TFA / DCM / rT
- f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

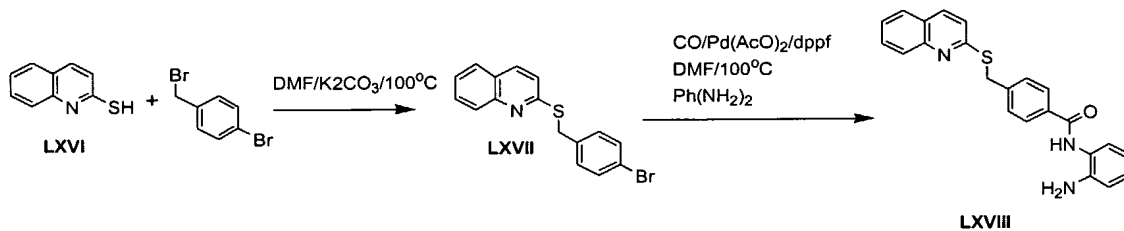
**[0115]** Compounds of formula (3), wherein  $X^2$  comprises a sulfur atom, and compounds of formula (4), wherein  $X^3$  comprises a sulfur atom, preferably may be prepared as outlined in Scheme 11. Bromide **LX** is converted to diaryl ester **LXI** using procedures analogous to those described for Scheme 6 above. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester **LXI** to the corresponding acid **LXIV**. Alternatively, ester **LXI** may be treated with chloroethylmorphonine, sodium iodide, potassium carbonate, triethylamine, and tetrabutylammonium iodide (TBAI) in DMF to produce ester **LXIII**, which is then converted to acid **LXIV** as in Scheme 1. Conversion of the acid **LXIV** to the anilinyll amide **LXV** is effected by procedures analogous to those set forth in Scheme 1 above.

Scheme 11



**[0116]** Alternatively, compounds of formula (3), wherein  $X^2$  comprises a sulfur atom, and compounds of formula (4), wherein  $X^3$  comprises a sulfur atom, may be prepared according to the procedures illustrated in Scheme 12. Sulfanyl anilinyll amide **LXVIII** is prepared using procedures analogous to those set forth in Schemes 3 and 5 above.

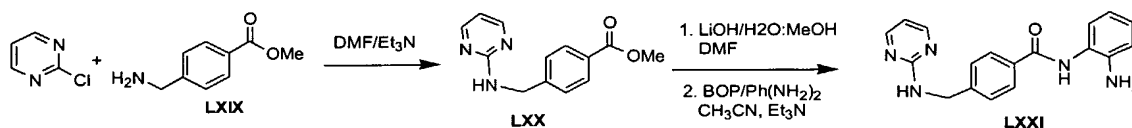
Scheme 12



**[0117]** Compounds of formula (3), wherein  $X^2$  comprises  $-N(R^9)-$ , and compounds of formula (4), wherein  $X^3$  comprises  $-N(R^{11})-$ , preferably may be prepared according to the synthetic route depicted

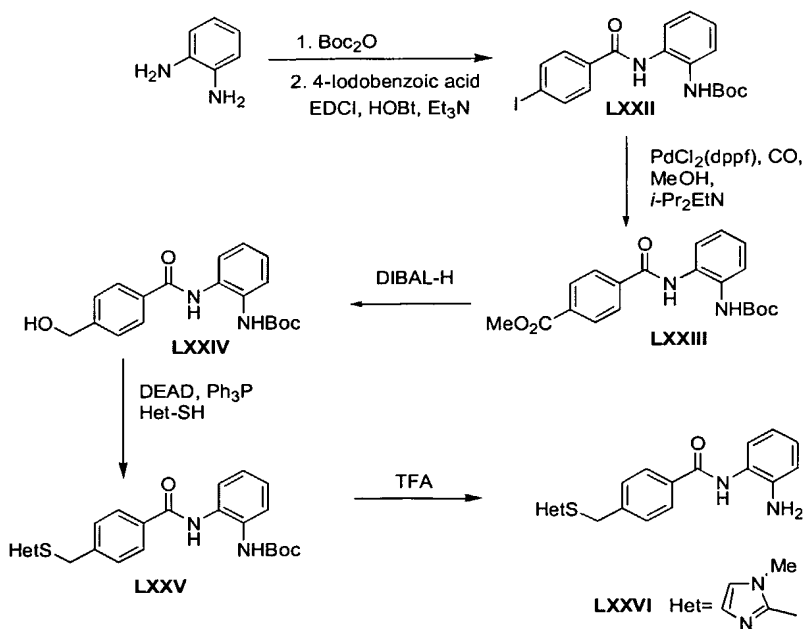
in Scheme 13. Amino aniliny amide **LXXI** is prepared according to synthetic steps similar to those described for Schemes 1 and 6 above.

Scheme 13



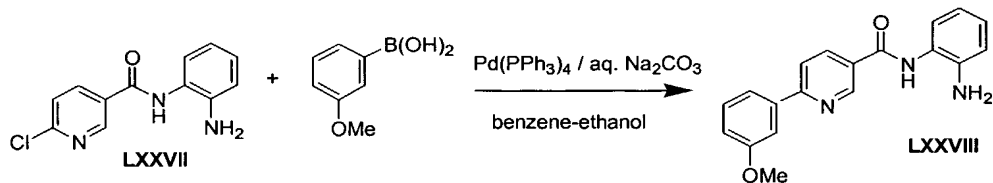
**[0118]** Compounds of formula (3), wherein  $X^2$  comprises a sulfur atom, and compounds of formula (4), wherein  $X^3$  comprises a sulfur atom, preferably may be prepared as outlined in Scheme 14. Phenylenediamine is reacted with di-tert-butyl dicarbonate, followed by iodobenzoic acid, dimethylaminopropylethylcarbodiimide, hydroxybenzotriazole, and triethylamine to provide protected aniliny amide **LXXII**. The iodide moiety of **LXXII** is converted to the methyl ester moiety of **LXXIII** using procedures analogous to those set forth for Scheme 3 above. The methyl ester moiety of **LXXIII** is converted to the hydroxyl moiety of **LXXIV** by treatment with a reducing agent such as diisobutylaluminum hydride (DIBAL-H). Addition of the heterocyclisulfhydryl compound Het-SH with triphenylphosphine and diethylazodicarboxylate converts the hydroxyl moiety of **LXXIV** to the sulfanyl moiety of **LXXV**. **LXXV** is deprotected with trifluoroacetic acid to afford the sulfanyl aniliny amide **LXXVI**.

Scheme 14



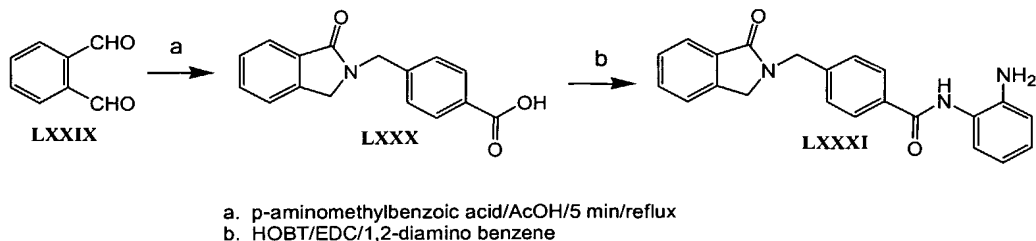
[0119] Compounds of formula (3), wherein  $X^2$  is a chemical bond, preferably may be prepared according to the synthetic route depicted in Scheme 15. Thus, chloroarylanilinyllamide **LXXVII** is treated with aryl boronic acid, benzene, ethanol, aqueous sodium carbonate, and triphenylphosphine palladium to afford the diarylanilinyllamide **LXXVIII**.

Scheme 15



[0120] Compounds such as **LXXXI** preferably may be prepared according to the procedures illustrated in Scheme 16. Thus, benzene-1,2-carbaldehyde **LXXIX** in acetic acid is treated with p-aminomethylbenzoic acid to produce the benzoic acid **LXXX**. The acid **LXXX** is converted to the corresponding anilinyllamide **LXXXI** by treatment with hydroxybenzotriazole, ethylenedichloride, and phenylenediamine.

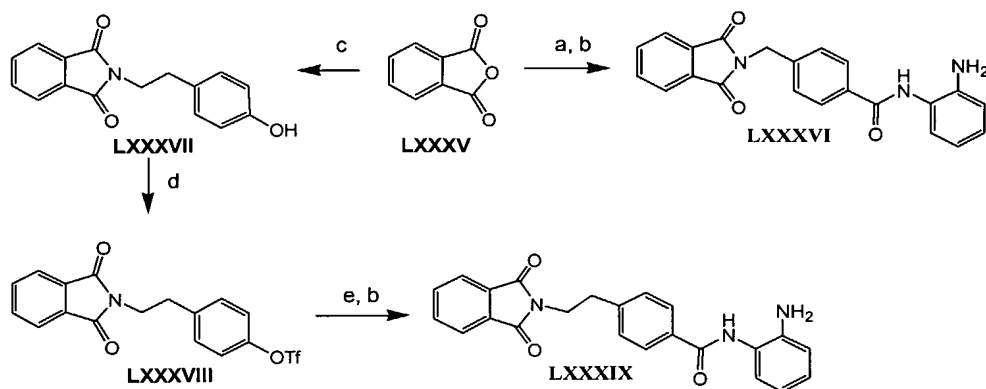
Scheme 16



[0121] Compounds such as **LXXXVI** and **LXXXIX** preferably may be prepared according to the procedures illustrated in Scheme 18. Phthalic anhydride **LXXXV** and p-aminomethylbenzoic acid are combined in acetic acid to produce an intermediate carboxylic acid, which is converted to the anilinyllamide **LXXXVI** using procedures analogous to those set forth in Schemes 15 and 16 above.

[0122] The addition of 4-(2-aminoethyl)phenol to phthalic anhydride **LXXXV** in acetic acid affords the hydroxyl compound **LXXXVII**. The hydroxyl group of **LXXXVII** is converted to the triflate group of **LXXXVIII** by treatment with sodium hydride, THF, DMF, and phenylaminoditriflate. Treatment of **LXXXVIII** according to procedures analogous to those described for Scheme 3 above affords the anilinyllamide **LXXXIX**.

Scheme 18



- a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs  
 b. HOBT/EDC/1,2-diamino benzene  
 c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux  
 d. PhNTf<sub>2</sub>/NaH/THF-DMF/30 min/0°C  
 e. 1. CO/Pd(OAc)<sub>2</sub>/dppf/Et<sub>3</sub>N/MeOH-DMF/4 days/75°C  
 2. AcOH/HCl/3 hrs/reflux

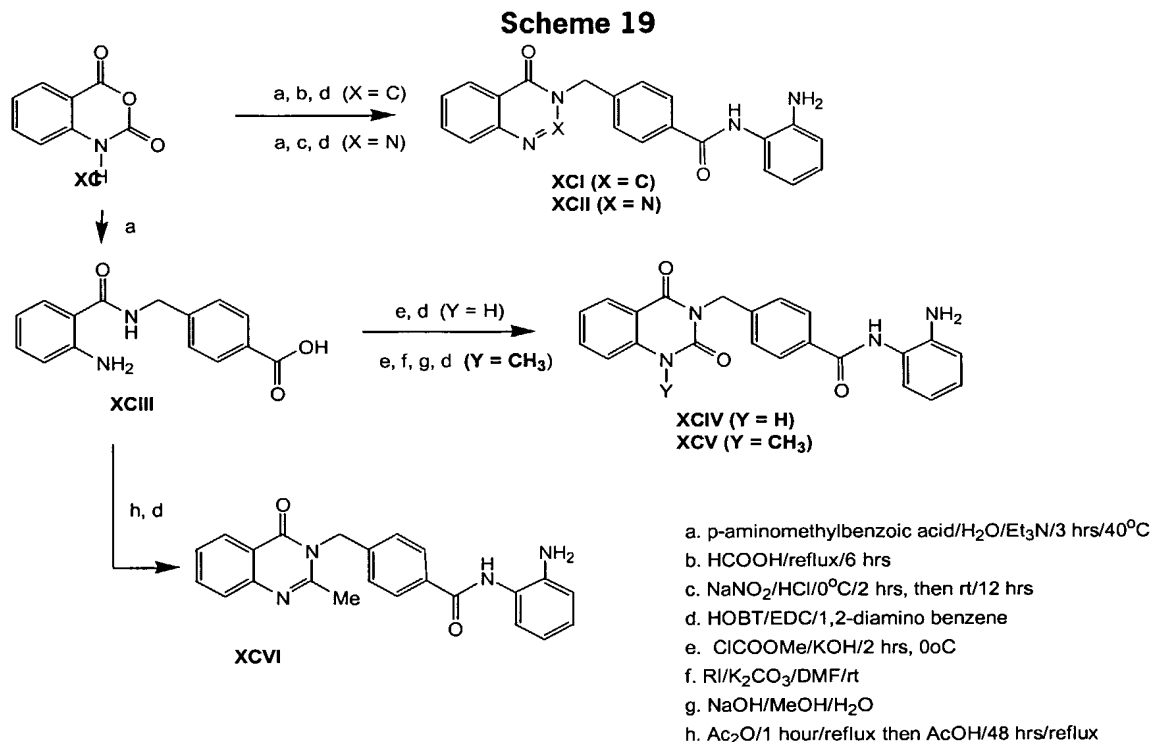
**[0123]** Compounds such as **XCi-XCvi** preferably may be prepared according to the synthetic route depicted in Scheme 19. Treatment of isatoic anhydride **XC** with p-aminomethylbenzoic acid in water and triethylamine, followed by formic acid affords an intermediate carboxylic acid, which is converted to anilinyllamide **XCi** using procedures analogous to those described for Scheme 16 above.

**[0124]** Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine, followed by hydrochloric acid and sodium nitrite affords an intermediate carboxylic acid, which is converted to anilinyllamide **XCii** using procedures analogous to those described for Scheme 16 above.

**[0125]** Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine affords benzoic acid **XCiii**. Treatment of **XCiii** with sodium hydroxide, dioxane, methylchloroformate, and methanol affords an intermediate quinazolidinedione carboxylic acid, the acid moiety of which is then converted to the anilinyllamide moiety of **XCiv** using procedures analogous to those described for Scheme 16 above. Alternatively, the intermediate quanzolinedione carboxylic acid in DMF is treated with potassium carbonate and methyl iodide to produce an intermediate benzoic acid methyl ester, which is converted to an intermediate benzoic acid by treatment with

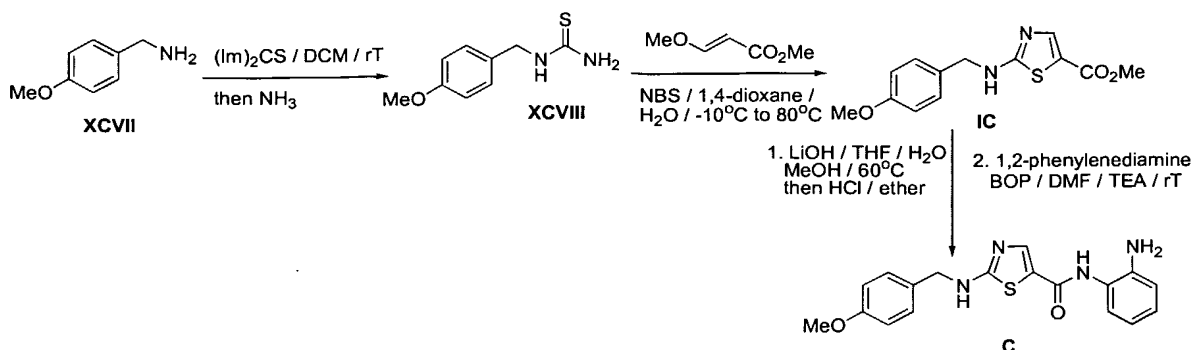
sodium hydroxide, methanol, and water. The benzoic acid is then converted to the corresponding anilinyllamide **XCIV** using procedures analogous to those described for Scheme 16 above.

**[0126]** Alternatively, treatment of **XCIII** with acetic anhydride followed by acetic acid produces an intermediate carboxylic acid, which is converted to anilinyllamide **XCVI** using procedures analogous to those described for Scheme 16 above.



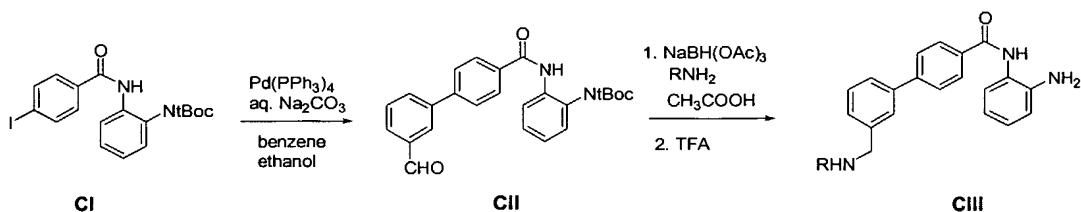
**[0127]** Compounds such as **C** preferably may be prepared as outlined in Scheme 20. Alkylamine **XCVII** is treated with thiocarbonyl diimidazole in dichloromethane, followed by ammonium hydroxide to afford thiourea **XCVIII**. Treatment of thiourea **XCVIII** with methylmethoxyacrylate in dioxane and N-bromosuccinimide produces thiazole ester **IC**. The ester **IC** is converted to the corresponding anilinyllamine **C** using procedures analogous to those set forth in Scheme 1 above.

## Scheme 20



**[0128]** Compounds of formula (3), wherein  $X^2$  is a chemical bond and  $\text{Cy}^3$  has an amino substituent preferably may be prepared according to the synthetic route depicted in Scheme 21. Thus, protected iodoarylanilinyamide CI is treated according to procedures analogous to those described for Scheme 15 above afford the diarylanilinyamide CII. The aldehyde moiety in CII is converted to the corresponding secondary amine moiety by treatment with the primary amine and sodium triacetoxyborohydride followed by glacial acetic acid. The resultant compound is deprotected to yield CIII using procedures analogous to those set forth in Scheme 3 above.

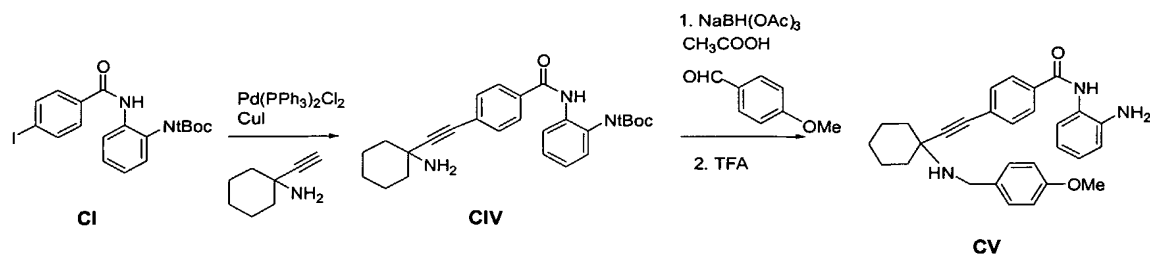
## Scheme 21



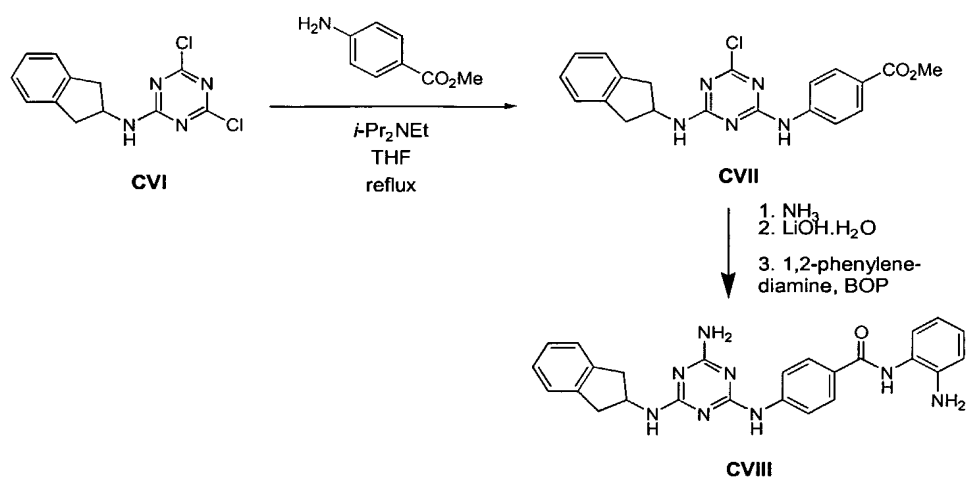
**[0129]** Compounds of formula (3), wherein  $X^2$  comprises an alkynylene moiety, and compounds of formula (4), wherein  $X^3$  comprises an alkynylene moiety, preferably may be prepared as outlined in Scheme 22. Treatment of protected iodoarylanilinyamide CI with triphenylphosphine palladium chloride, cuprous iodide, and 1-ethynylcyclohexylamine affords the alkynylarylanilinyamide CIV. The primary amine moiety in CIV is converted to the corresponding secondary amine and the aniline moiety is deprotected to afford CV using procedures analogous to those described for Scheme 21 above.



## Scheme 22

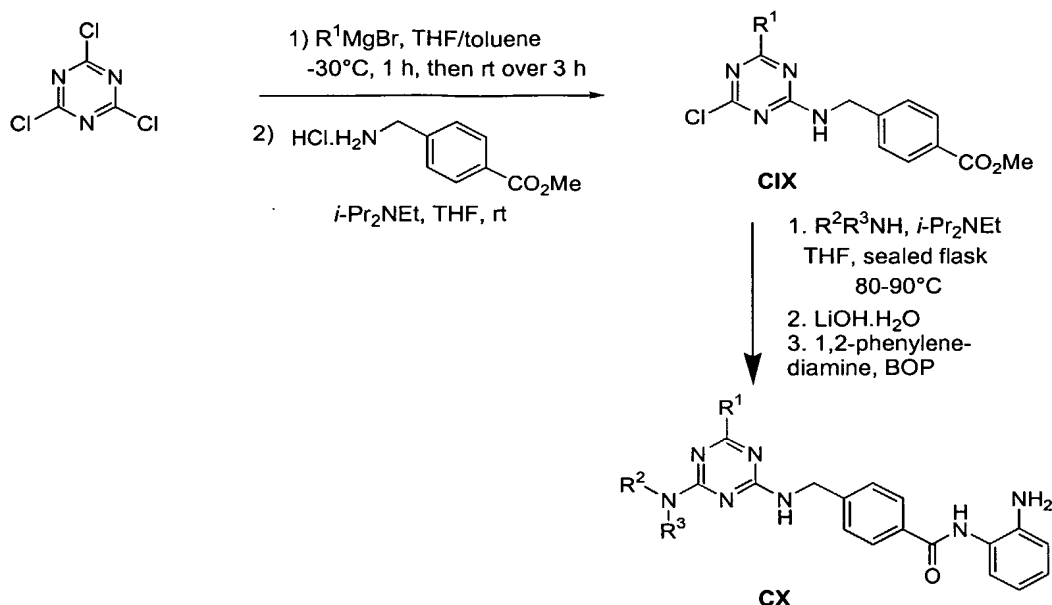


## Scheme 24



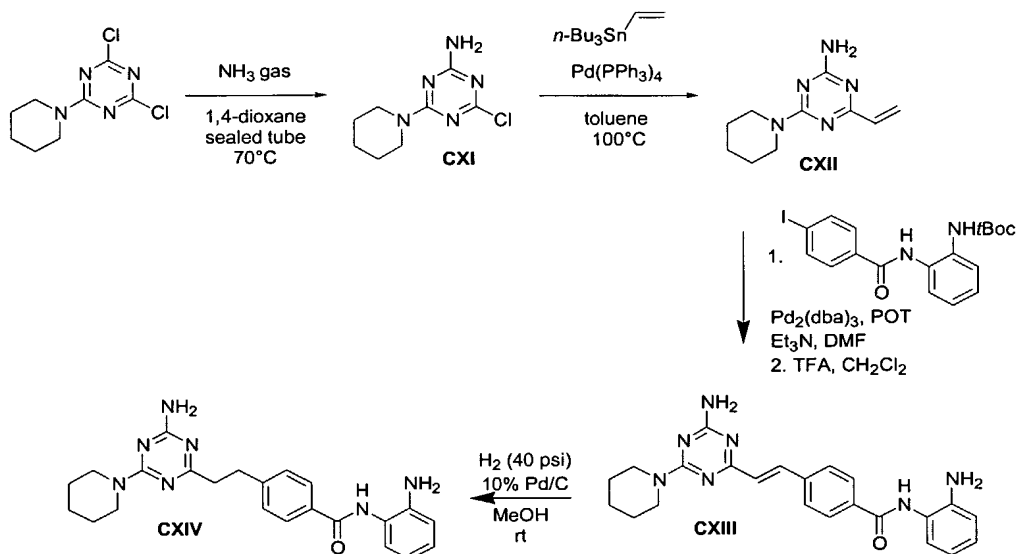
**[0130]** Compounds such as **CVIII** preferably may be prepared according to the synthetic route depicted in Scheme 24. Dichloroaminotriazine **CVI** is treated with methyl-4-aminobenzoate in the presence of diisopropylethylamine to produce diaminotriazine **CVII**. Addition of ammonia gas and dioxane, followed by a saponification and a peptide coupling using the same procedures analogous to those described for Scheme 1 above.

Scheme 30



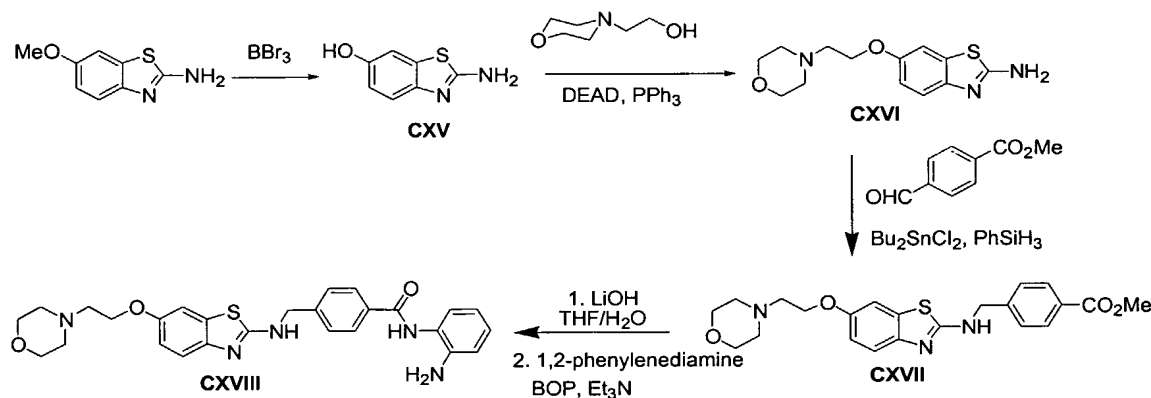
[0131] Compounds such as **CX** preferably may be prepared according to the synthetic route depicted in Scheme 30. The Grignard reaction of trichloroaminotriazine with various alkyl magnesium bromide, followed by a treatment with methyl-4-aminobenzoate in the presence of diisopropylethylamine yields alkylaminotriazine **CIX**. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester **CIX** to the corresponding aniliny amide **CX**.

Scheme 32



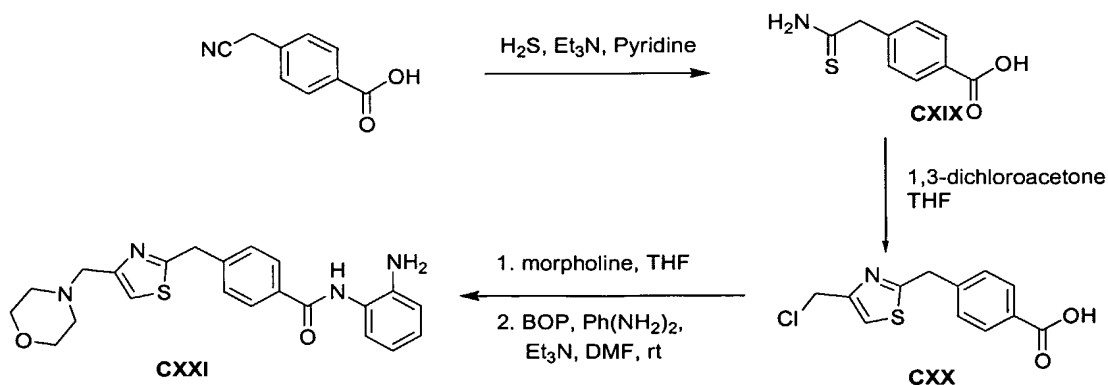
[0132] Amination of dichlorotriazine proceeded using the usual condition described in Scheme 1 to afford **CXI**. Still coupling using vinyl stannane provides **CXII**. Treatment with protected iodoanilide, triethylamine, POT and dibenzylacetone palladium then yields anilinyamide, which is deprotected with trifluoroacetic acid to provide the alkene **CXIII**. Hydrogenation of the alkene affords the final compound **CXIV**.

Scheme 33



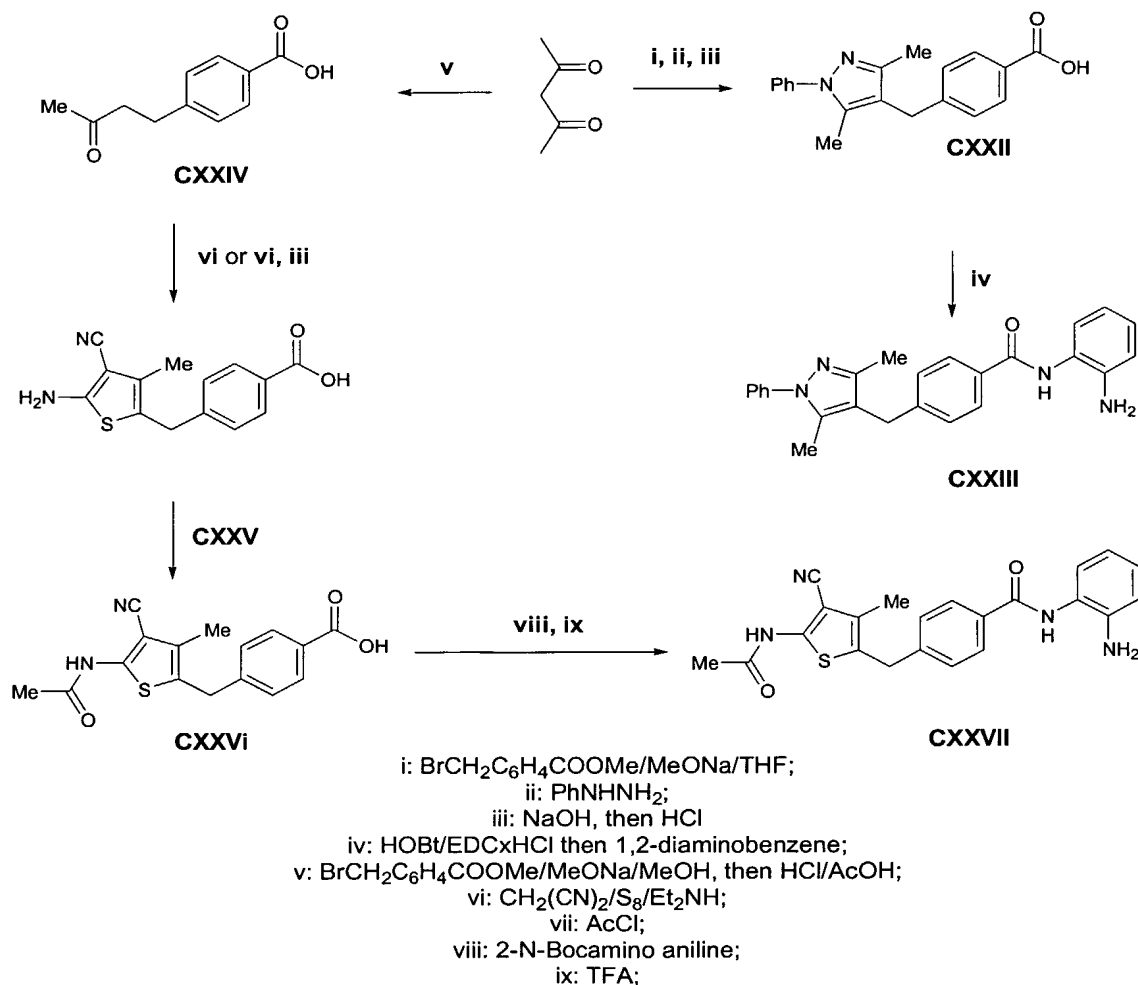
[0133] Compounds such as **CXVIII** preferably may be prepared according to the synthetic route depicted in Scheme 33. Treatment of methoxyaminobenzothiazole with tribromide boron affords the corresponding acid **CXV**. Mitsunobu reaction using hydroxyethyl morpholine in the presence of diethylazodicarboxylate and triphenylphosphine yields the amine **CXVI**. Reductive amination with methyl-4-formylbenzoate using phenylsilane and tin catalyst yields to the ester **CXVII**. Saponification followed by the usual peptide coupling analogous to those describe for Scheme 1 above provides the desired anilide **CXVIII**.

Scheme 42



[0134] Treatment 4-methylcyanobenzoic acid with hydrogen sulfide affords **CXXIX**, which is subjected to cyclization in the presence of 1,3-dichloroacetone to yield **CXX**. Treatment with morpholine followed by a peptide coupling using the standard condition produces **CXXI**.

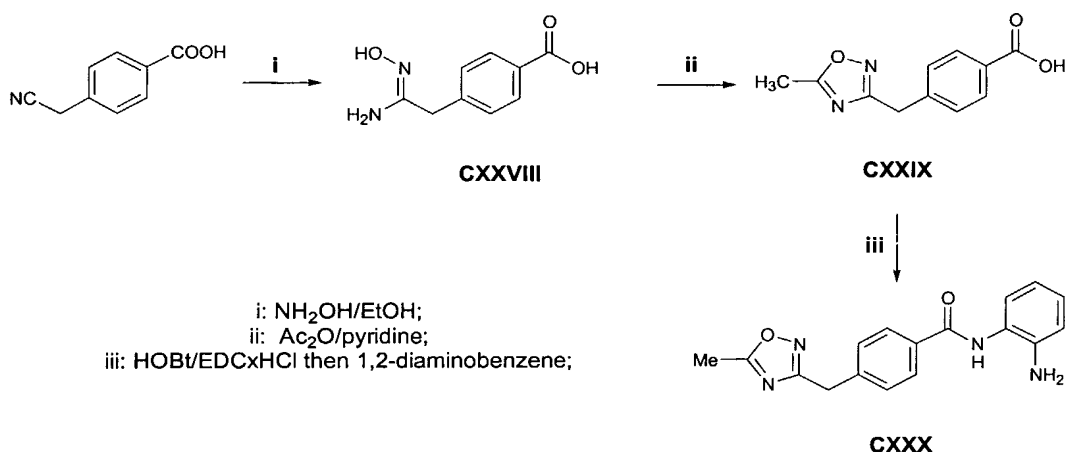
Scheme 49



[0135] Compounds such as **CXXIII** and **CXXVII** preferably may be prepared according to the synthetic scheme 49. Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of  $\text{NaOMe}$  and phenyl hydrazine followed by saponification, afforded the intermediate acid **CXXII**. This material was coupled with 1,2-diaminobenzene in a standard fashion to afford **CXXIII**.

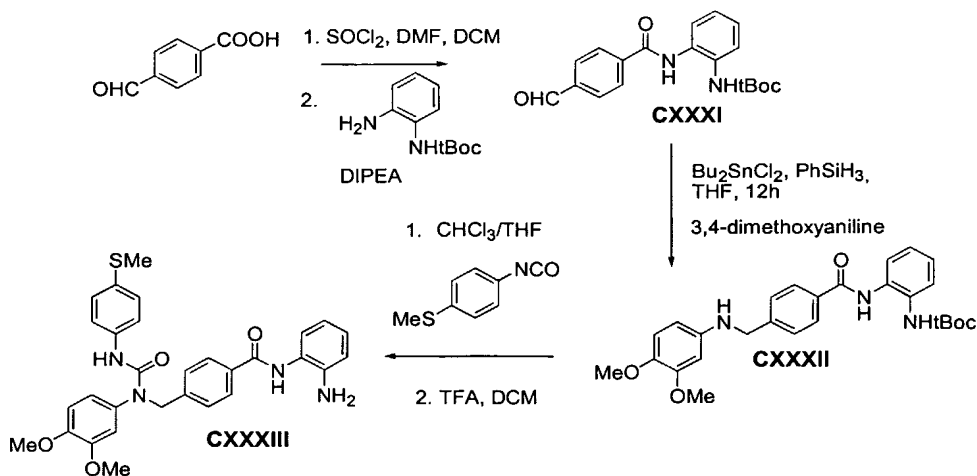
[0136] Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and a 1:1 mixture AcOH-HCl (conc.) afforded the intermediate acid **CXXIV**. This keto-acid reacting with sulfur and malonodinitrile in the presence of a base, produced the thiophene **CXXV**, which was converted into the desired **CXXVII** using standard procedures.

Scheme 50



[0137] Compounds such as CXXX preferably may be prepared according to the synthetic scheme 50. Treatment of 4-cyanomethylbenzoic acid with hydroxylamine produced the amidoxime CXXVIII, which upon treatment with acetic anhydride was converted into the oxadiazole CXXIX. The latter was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXX.

Scheme 57



[0138] Compounds such as CXXXIII preferably may be prepared according to the synthetic route depicted in Scheme 57. Treatment of 4-formylbenzoic acid with thionyl chloride afford the acyl

chloride which is coupled with protected anilide to produce CXXXI. Reductive amination with dimethoxyaniline using phenylsilane and tin catalyst yields to the protected anilide CXXXII. Treatment with isocyanate followed by deprotection with trifluoroacetic acid provides the ureidoanilide CXXXIII.

### **Pharmaceutical Compositions**

**[0139]** In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

**[0140]** The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

**[0141]** As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula  $-NR + Z^-$ , wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate,

or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

**[0142]** The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

#### **Inhibition of Histone Deacetylase**

**[0143]** In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study of the role of histone deacetylase in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

**[0144]** Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., **265**: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton et al., Science, **272**: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

**[0145]** In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-

4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.

**[0146]** Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

**[0147]** Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

**[0148]** The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.



**[0149]** In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

**[0150]** In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

**[0151]** The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

**[0152]** It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

**[0153]** The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

**[0154]** The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

**[0155]** When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01  $\mu\text{M}$  to about 100  $\mu\text{M}$ , more preferably from about 0.05  $\mu\text{M}$  to about 50  $\mu\text{M}$ , still more preferably from about 0.1  $\mu\text{M}$  to about 25  $\mu\text{M}$ , and still yet more preferably from about 0.5  $\mu\text{M}$  to about 25  $\mu\text{M}$ . For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

**[0156]** In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC7, and/or HDAC-8 (see e.g., GenBank Accession Number U50079

for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

**[0157]** For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

**[0158]** For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

**[0159]** Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

**[0160]** For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos.

5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

**[0161]** For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

**[0162]** The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) *Proc. Natl. Acad. Sci. USA* 94: 684-689.

**[0163]** Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) *Methods in Molec. Biol.* 20: 465-496).

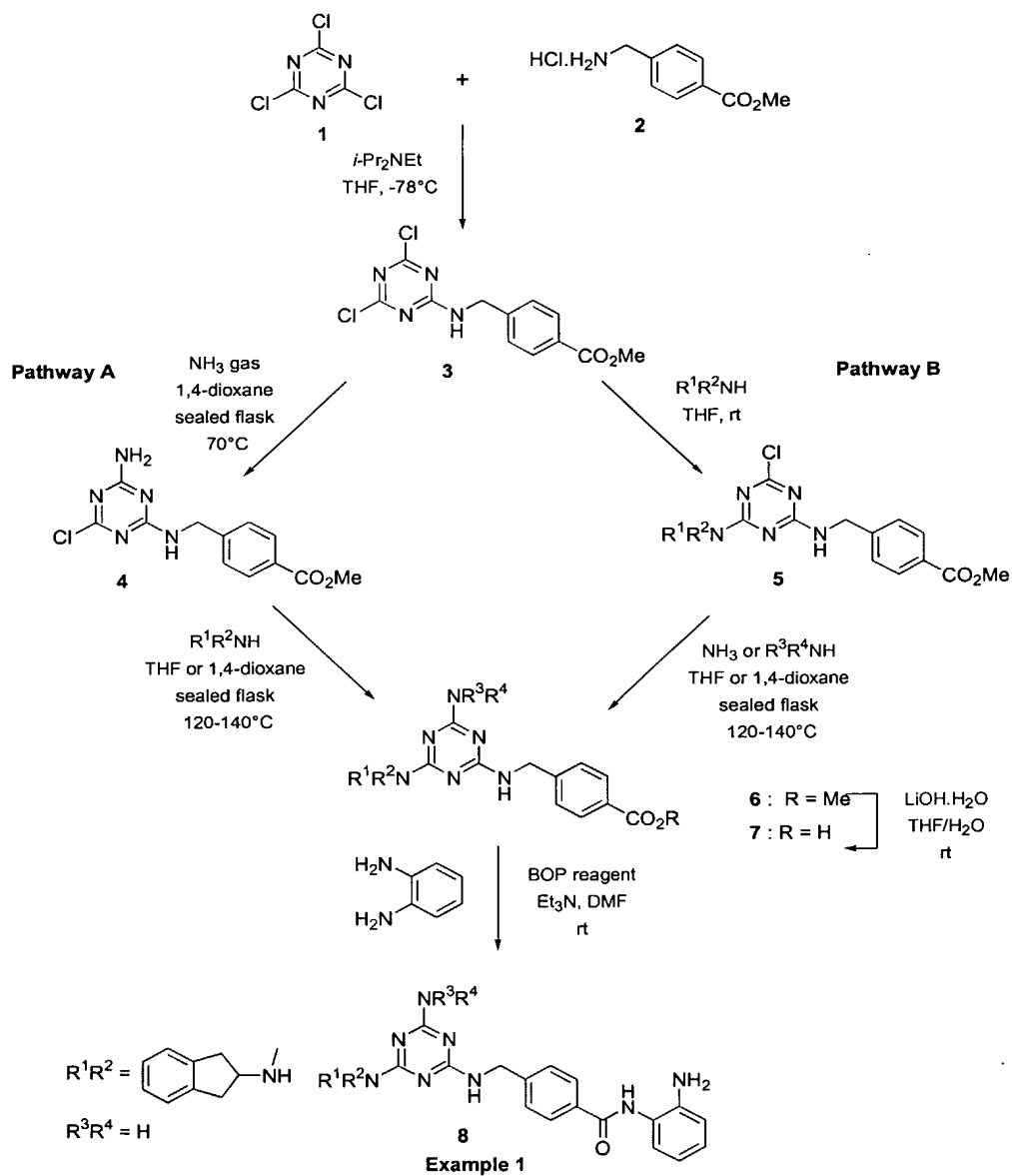
**[0164]** Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table 1.

Table 1

| Oligo     | Target      | Accession Number | Nucleotide Position | Sequence                    | position within Gene |
|-----------|-------------|------------------|---------------------|-----------------------------|----------------------|
| HDAC1 AS1 | Human HDAC1 | U50079           | 1585-1604           | 5'-GAAACGTGAGGGACTCAGCA-3'  | 3'-UTR               |
| HDAC1 AS2 | Human HDAC1 | U50079           | 1565-1584           | 5'-GGAAGCCAGAGCTGGAGAGG-3'  | 3'-UTR               |
| HDAC1 MM  | Human HDAC1 | U50079           | 1585-1604           | 5'-GTTAGGTGAGGCACCTGAGGA-3' | 3'-UTR               |
| HDAC2 AS  | Human HDAC2 | U31814           | 1643-1622           | 5'-GCTGAGCTGTTCTGATTTGG-3'  | 3'-UTR               |
| HDAC2 MM  | Human HDAC2 | U31814           | 1643-1622           | 5'-CGTGAGCACCTTCTCATTTC-3'  | 3'-UTR               |
| HDAC3 AS  | Human HDAC3 | AF039703         | 1276-1295           | 5'-CGCTTTCCCTTGTCATTGACA-3' | 3'-UTR               |
| HDAC3 MM  | Human HDAC3 | AF039703         | 1276-1295           | 5'-GCCTTTCCCTACTCATTGTGT-3' | 3'-UTR               |
| HDAC4 AS1 | Human HDAC4 | AB006626         | 514-33              | 5'-GCTGCCCTGCCGTGCCACCC-3'  | 5'-UTR               |
| HDAC4 MM1 | Human HDAC4 | AB006626         | 514-33              | 5'-CGTGCCCTGCGCTGCCACGG-3'  | 5'-UTR               |
| HDAC4 AS2 | Human HDAC4 | AB006626         | 7710-29             | 5'-TACAGTCCCATGCAACCTCCA-3' | 3'-UTR               |
| HDAC4 MM4 | Human HDAC4 | AB006626         | 7710-29             | 5'-ATCAGTCCCAACCAACCTCGT-3' | 3'-UTR               |
| HDAC5 AS  | Human HDAC5 | AF039691         | 2663-2682           | 5'-CTTCGGTCTCACCTGCTTGG-3'  | 3'-UTR               |
| HDAC6 AS  | Human HDAC6 | AJ011972         | 3791-3810           | 5'-CAGGCTGGAATGAGCTACAG-3'  | 3'-UTR               |
| HDAC6 MM  | Human HDAC6 | AJ011972         | 3791-3810           | 5'-GACGCTGCAATCAGGTAGAC-3'  | 3'-UTR               |
| HDAC7 AS  | Human HDAC7 | AF239243         | 2896-2915           | 5'-CTTCAGCCAGGATGCCCAACA-3' | 3'-UTR               |
| HDAC8 AS1 | Human HDAC8 | AF230097         | 51-70               | 5'-CTCCGGCTCCTCCATCTTCC-3'  | 5'-UTR               |
| HDAC8 AS2 | Human HDAC8 | AF230097         | 1328-1347           | 5'-AGCCAGCTGCCCACTTGATGC-3' | 3'-UTR               |

**[0165]** The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

### EXAMPLES



### Example 1

#### **4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (compound 8)**

##### Step 1: Methyl-4-[(4,6-dichloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 3)

**[0166]** To a stirred solution at  $-78^{\circ}\text{C}$  of cyanuric chloride **1** (8.23 g, 44.63 mmol) in anhydrous THF (100 mL) under nitrogen was added a suspension of methyl 4-(aminomethyl)benzoate.HCl **2** (10.00 g, 49.59 mmol), in anhydrous THF (50 mL), followed by  $i\text{-Pr}_2\text{NEt}$  (19.00 mL, 109.10 mmol). After 30 min, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ $\text{CH}_2\text{Cl}_2$ : 5/95) to afford the title compound **3** (12.12 g, 38.70 mmol, 87% yield) as a pale yellow solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): AB system ( $\delta_{\text{A}} = 8.04$ ,  $\delta_{\text{B}} = 7.38$ ,  $J = 8.5$  Hz, 4H), 6.54 (bt, 1H), 4.76 (d,  $J = 6.3$  Hz, 2H), 3.93 (s, 3H).

##### Pathway A

##### Step 2: Methyl-4-[(4-amino-6-chloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 4)

**[0167]** In a 150 mL sealed flask, a solution of **3** (6.00 g, 19.16 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with  $\text{NH}_3$  gas for 5 min, and warmed to  $70^{\circ}\text{C}$  for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with  $\text{NH}_3$  gas was repeated at room temperature for 5 min, and the reaction mixture was warmed to  $70^{\circ}\text{C}$  again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ $\text{CH}_2\text{Cl}_2$ : 30/70) to afford the title compound **4** (5.16 g, 17.57 mmol, 91% yield) as a white solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): AB system ( $\delta_{\text{A}} = 8.01$ ,  $\delta_{\text{B}} = 7.35$ ,  $J = 8.1$  Hz, 4H), 5.79 (bs, 1H), 5.40-5.20 (m, 2H), 4.72-4.63 (m, 2H), 3.91 (s, 3H).

Pathway BStep 2: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound **5**)

**[0168]** To a stirred solution at room temperature of **3** (3.00 g, 9.58 mmol) in anhydrous THF (50 mL) under nitrogen were added *i*Pr<sub>2</sub>NEt (8.34 mL, 47.90 mmol) and 2-aminoindan.HCl (1.95 g, 11.50 mmol) or R<sup>1</sup>R<sup>2</sup>NH (1.2 equiv), respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to afford the title compound **5** (4.06 g, 9.91 mmol, quantitative yield) as a white powder. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): mixture of rotamers, 8.06-7.94 (m, 2H), 7.43-7.28 (m, 2H), 7.24-7.12 (m, 4H), 6.41 and 6.05 (2 bt, 1H), 5.68-5.44 (m, 1H), 4.92-4.54 (m, 3H), 3.92 (bs, 3H), 3.41-3.12 (m, 2H), 2.90-2.70 (m, 2H).

Step 3: Methyl-4-[(4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound **6**)General procedure for the amination with NH<sub>3</sub> gas:

**[0169]** In a 150 mL sealed flask, a solution of **5** (3.90 g, 9.51 mmol) in anhydrous 1,4-dioxane (80 mL) was stirred at room temperature, saturated with NH<sub>3</sub> gas for 5 min, and warmed to 140°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH<sub>3</sub> gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub>: 3/97) to afford the title compound **6** (3.50 g, 8.96 mmol, 94% yield) as a pale yellow sticky solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.99 (bd, J = 8.2 Hz, 2H), 7.41-7.33 (m, 2H), 7.24-7.13 (m, 4H), 5.50-5.00 (m, 2H), 4.90-4.55 (m, 5H), 3.92 (s, 3H), 3.40-3.10 (m, 2H), 2.90-2.70 (m, 2H). <sup>13</sup>C NMR: (75 MHz, CDCl<sub>3</sub>) δ (ppm): 166.88, 167.35, 166.07, 144.77, 141.07, 129.82, 128.93, 127.01, 126.61, 124.70, 52.06, 51.80, 44.25, 40.16. HRMS (calc.): 390.1804, (found): 390.1800.

Pathways A and B, step 3, general procedure with primary and/or secondary amines:

**[0170]** In a 50-75 mL sealed flask, a stirred solution of **4** (500 mg, 1.70 mmol, 1 equiv), *i*Pr<sub>2</sub>NEt (1.48 mL, 8.51 mmol, 5 equiv) and R<sup>1</sup>R<sup>2</sup>NH or R<sup>3</sup>R<sup>4</sup>NH (1.5-3 equiv) in anhydrous THF or 1,4-dioxane (20-30 mL) was warmed to 120-140°C for 15-24 h. Then, the reaction mixture was allowed to cool



to room temperature, poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel to afford the title compound.

Step 4: 4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (compound 7)

**[0171]** To a stirred solution at room temperature of **6** (2.07 g, 5.30 mmol) in THF (50 mL) was added a solution of  $\text{LiOH}\cdot\text{H}_2\text{O}$  (334 mg, 7.96 mmol) in water (25 mL). After 18 h, the reaction mixture was diluted in water and acidified with 1 N HCl until pH 5-6 in order to get a white precipitate. After 1 h, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **7** (1.73 g, 4.60 mmol, 87% yield) as a white solid.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 8.05 (bd,  $J = 8.1$  Hz, 2H), 7.56-7.42 (m, 2H), 7.30-7.10 (m, 4H), 5.90-5.65 (m, 2H), 4.85-4.60 (m, 4H), 3.40-2.80 (m, 4H). HRMS (calc.): 376.1648, (found): 376.1651.

Step 5: 4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-N-(2-amino-phenyl)-benzamide (compound 8)

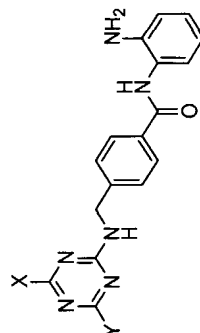
**[0172]** To a stirred solution at room temperature of **7** (200 mg, 0.53 mmol) in anhydrous DMF (5 mL) under nitrogen were added  $\text{Et}_3\text{N}$  (74  $\mu\text{L}$ , 0.53 mmol) and BOP reagent (282 mg, 0.64 mmol), respectively. After 40 min, a solution of 1,2-phenylenediamine (64 mg, 0.58 mmol),  $\text{Et}_3\text{N}$  (222  $\mu\text{L}$ , 1.59 mmol) in anhydrous DMF (2 mL) was added dropwise. After 1.5 h, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/ $\text{CH}_2\text{Cl}_2$ : 2/98 $\rightarrow$ 5/95) to afford the title compound **8** (155 mg, 0.33 mmol, 63% yield) as a pale yellow foam.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 9.04 (bs, 1H), 7.96 (bd,  $J = 8.0$  Hz, 2H), 7.50-7.40 (m, 2H), 7.30 (dd,  $J = 8.0$  Hz, 1.4 Hz, 1H), 7.22-7.08 (m, 4H), 6.99 (ddd,  $J = 8.0$  Hz, 7.5 Hz, 1.5 Hz, 1H), 6.86 (dd,  $J = 8.0$  Hz, 1.4 Hz, 1H), 6.67 (dt,  $J = 7.5$  Hz, 1.4 Hz, 1H), 6.60-5.49 (m, 4H), 4.80-4.50 (m, 4H), 3.30-3.08 (m, 2H), 2.96-2.74 (m, 2H).

## EXAMPLES 2-28

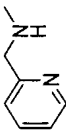
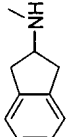
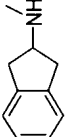
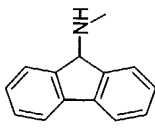
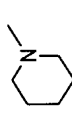

**[0173]** Examples 2 to 28 describe the preparation of compounds **9** to **35** using the same procedure as described for compound **8** of Example 1. Characterization data are presented in Tables 2a and 2b.

Table 2a

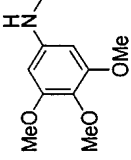
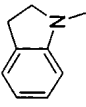
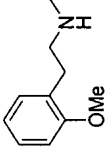
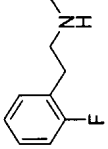
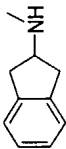
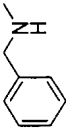
## Characterization of Compounds Prepared in Examples 2-28



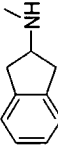
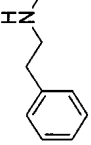

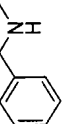

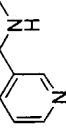


| Ex. | Cpd | Y | X               | Name  | Characterization   | Schm |
|-----|-----|---|-----------------|---|--|------|
| 2   | 9   |   | NH <sub>2</sub> | 4-[(4-amino-6-morpholin-4-yl-[1,3,5]-triazin-2-ylamino)methyl]-N-(2-amino-phenyl)-benzamide           | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.31 (m, 1H), 7.08 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.82 (t, J = 6.7 Hz, 2H), 5.62 (t, J = 5.9 Hz, 1H), 4.90 (bs, 2H), 4.61 (d, J = 6.0 Hz, 2H), 3.75-3.62 (m, 10H).   | 1A   |
| 3   | 10  |   | NH <sub>2</sub> | 4-[(4-amino-6-(1-indanyl-amino)-[1,3,5]-triazin-2-ylamino)methyl]-N-(2-amino-phenyl)-benzamide        | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.05-7.95 (m, 2H), 7.55-7.45 (m, 2H), 7.37-7.10 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.55 (m, 5H), 4.75-4.60 (m, 3H), 3.05-2.75 (m, 2H), 2.60-2.45 (m, 1H), 2.00-1.84 (m, 1H). HRMS (calc.): 466.2229, (found): 466.2225  | 1A   |
| 4   | 11  |   | NH <sub>2</sub> | N-(2-Amino-phenyl)-4-[(4-amino-6-(4-phenyl-piperazin-1-yl)-[1,3,5]triazin-2-ylamino)methyl]-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.05-9.00 (m, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.93 (s), 7.84 (d, J = 8.0 Hz), 7.72 (d, J = 8.2 Hz), 7.58-7.40 (m, 3H), 7.31-7.19 (m, 3H), 7.12-7.05 (m), 6.98 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.80 (t, J = 7.1 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.57-6.50 (m, 1H), 5.78-5.60 (m, 2H), 4.67-4.64 (m, 2H), 3.88-3.84 (m, 4H), 3.14 (s, 4H). HRMS (calc.): 477.2389 [M <sup>+</sup> - NH <sub>4</sub> ], (found): 477.2383 | 1A   |

| Ex. | Cpd | Y   | X   | Name   | Characterization   | Schm |
|-----|-----|---|---|--|--|------|
| 5   | 12  |    | NH <sub>2</sub>   | 4-[[4-amino-6-(2-pyridinyl-methyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.08 (bs, 1H), 8.51 (bs, 1H), 8.05-7.90 (m, 2H), 7.80-7.60 (m, 1H), 7.55-7.15 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85-6.55 (m, 1H), 5.84 (bs, 2H), 4.75-4.60 (m, 4H). HRMS (calc.): 441.2025, (found): 441.2029                 | 1A   |
| 6   | 13  |    |  | 4-[[4,6-bis(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide             | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.08 (bs, 1H), 8.05-7.95 (m, 2H), 7.56-7.44 (m, 2H), 7.34 (bd, J = 7.7 Hz, 1H), 7.27-7.10 (m, 8H), 7.04 (td, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.90 (m, 3H), 4.90-4.58 (m, 6H), 3.40-2.80 (m, 4H). HRMS (calc.): 582.2855, (found): 582.2838 | 1B   |
| 7   | 14  |    | NH <sub>2</sub>   | 4-[[4-Amino-6-(9H-fluoren-9-ylamino)-[1,3,5]triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide      | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.05-9.00 (m, 1H), 8.03-7.87 (m, 2H), 7.80-7.70 (m, 2H), 7.63-7.20 (m, 9H), 7.00 (t, 1H), 6.86 (d, 1H), 6.66 (t, 1H), 6.50-5.50 (m, 6H), 4.75-4.55 (m, 3H). HRMS (calc.): 514.2229, (found): 514.2232  | 1B   |
| 8   | 15  |   | NH <sub>2</sub>   | N-(2-amino-phenyl)-4-[[4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-ylamino)-methyl]-benzamide              | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.96 (bs, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.08 (dt, J = 7.7 Hz, 1.4 Hz, 1H), 6.83 (t, J = 6.6 Hz, 2H), 5.47 (bs, 1H), 4.80 (bs, 2H), 4.60 (d, J = 6.0 Hz, 2H), 3.88 (bs, 2H), 3.67 (t, J = 5.2 Hz, 4H), 1.66-1.58 (m, 2H), 1.56-1.48 (m, 4H).                    | 1A   |
| 9   | 16  |  | NH <sub>2</sub>   | 4-[[4-amino-6-cyclopentyl-amino-[1,3,5]triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide           | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.97 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.39-7.34 (m, 3H), 7.10 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85 (t, J = 7.0 Hz, 2H), 5.56 (bs, 1H), 4.90 (bs, 3H), 4.62 (s, 2H), 4.25-4.19 (m, 1H), 3.88 (bs, 2H), 1.95 (m, 2H), 1.71-1.59 (m, 4H), 1.43-1.37 (m, 2H).  | 1A   |

| Ex. | Cpd | Y | X               | Name  | Characterization  | Schm |
|-----|-----|---|-----------------|---|---|------|
| 10  | 17  |   | NH <sub>2</sub> | (1 <i>R</i> )-4-[(4-amino-6-(2-exo-fenchyl-amino)-[1,3,5]-triazin-2-ylamino)methyl]-N(2-amino-phenyl)-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.08 (bs, 1H), AB system (δ <sub>A</sub> = 8.00, δ <sub>B</sub> = 7.51, J = 8.0 Hz, 4H), 7.33 (bd, J = 7.7 Hz, 1H), 7.03 (ddd, J = 8.0 Hz, 7.3 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-6.28 (m, 1H), 5.80-5.20 (m, 3H), 4.67 (bs, 4H), 3.87 (bd, J = 9.1 Hz, 1H), 1.80-1.60 (m, 4H), 1.56-1.42 (m, 1H), 1.34-1.00 (m including 2 s, 8H), 0.84 (s, 3H).<br>HRMS (calc.): 486.2855, (found): 486.2844 | 1A   |
| 11  | 18  |   |                 | 4-[(4-allyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino)methyl]-N(2-amino-phenyl)-benzamide             | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.4 Hz, 2H), 7.58-7.42 (m, 2H), 7.34 (bd, J = 8.0 Hz, 1H), 7.27-7.10 (m, 4H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-5.70 (m, 3H), 5.26-5.00 (m, 2H), 4.86-4.54 (m, 4H), 4.10-3.90 (m, 2H), 3.38-3.10 (m, 2H), 3.00-2.80 (m, 2H).<br>HRMS (calc.): 506.2542, (found): 506.2533   | 1B   |
| 12  | 19  |   |                 | 4-[(4-cyclopropyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino)methyl]-N(2-amino-phenyl)-benzamide       | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.7 Hz, 2H), 7.60-7.40 (m, 2H), 7.33 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.28-7.10 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.3 Hz, 1H), 6.67-5.80 (m, 2H), 4.90-4.50 (m, 4H), 3.40-3.10 (m, 2H), 3.05-2.70 (m, 3H), 0.75-0.43 (m, 4H).<br>HRMS (calc.): 506.2542, (found): 506.2548   | 1B   |
| 13  | 20  |   | NH <sub>2</sub> | 4-[(4-Amino-6-phenethylamino-[1,3,5]triazin-2-ylamino)methyl]-N(2-amino-phenyl)-benzamide                       | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.03 (s, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.99 (td, J = 8.0 Hz, 1.3 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.62-5.40 (m, 5H), 4.75-4.45 (m, 3H), 3.59-3.45 (m, 2H), 2.95-2.70 (m, 2H).<br>HRMS (calc.): 454.2229, (found): 454.2235   | 1A   |

| Ex. | Cpd | Y   | X   | Name   | Characterization   | Schm |
|-----|-----|---|---|--|--|------|
| 14  | 21  |    | NH <sub>2</sub>   | N-(2-Amino-phenyl)-4-([4-amino-6-(3,4,5-trimethoxy-phenylamino)-[1,3,5]triazin-2-ylamino]-methyl)-benzamide    | <sup>1</sup> H NMR (CDCl <sub>3</sub> /MeOD) δ (ppm): 7.72 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 7.7 Hz, 1H), 6.91 (td, J = 7.7 Hz, 1.2 Hz, 1H), 6.70-6.61 (m, 4H), 4.61 (bs, 2H), 3.58-3.52 (m, 9H).  | 1B   |
| 15  | 22  |    | NH <sub>2</sub>   | 4-([4-Amino-6-(2,3-dihydro-indol-1-yl)-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide          | <sup>1</sup> H NMR (CDCl <sub>3</sub> /MeOD) δ (ppm): 8.06 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.02-6.96 (m, 2H), 6.84-6.71 (m, 3H), 4.61 (bs, 2H), 4.03 (t, J = 8.5 Hz, 2H), 3.02 (t, J = 8.5 Hz, 2H).  | 1B   |
| 16  | 23  |    | NH <sub>2</sub>   | 4-([4-Amino-6-[2-(2-methoxy-phenyl)-ethylamino]-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.06 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.21-6.70 (m, 6H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-5.70 (m, 5H), 4.75-4.55 (m, 3H), 3.81 (s, 3H), 3.55-3.45 (m, 2H), 2.90-2.78 (m, 2H). HRMS (calc.): 484.2335, (found): 484.2331               | 1A   |
| 17  | 24  |   | NH <sub>2</sub>   | 4-([4-Amino-6-[2-(2-fluoro-phenyl)-ethylamino]-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide  | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.03 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.38-7.17 (m, 2H), 7.17-6.95 (m, 4H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (t, J = 7.0 Hz, 1H), 6.50-5.60 (m, 5H), 4.75-4.55 (m, 3H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H). HRMS (calc.): 472.2135, (found): 472.2146 | 1A   |
| 18  | 25  |  |  | 4-([4-benzyl-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide          | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.06 (bs, 1H), 8.04-7.93 (m, 2H), 7.57-7.12 (m, 12H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.72 (bt, J = 7.6 Hz, 1H), 6.68-5.90 (m, 3H), 4.84-4.50 (m, 7H), 3.35-3.13 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 556.2699, (found): 556.2706                             | 1B   |

| Ex. | Cpd | Y   | X   | Name  | Characterization   | Schm |
|-----|-----|---|---|---|--|------|
| 19  | 26  |    |    | N-(2-Amino-phenyl)-4-[[4,6-di-piperidin-1-yl-[1,3,5]triazin-2-ylamino]-methyl]-benzamide                            | <sup>1</sup> H NMR: (CDCl <sub>3</sub> ) δ (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz, 8H), 1.63-1.53 (m, 12H).  | 1B   |
| 20  | 27  |    |    | 4-[[6-(2-indanyl-amino)-4-phenethyl-amino-[1,3,5]triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide            | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.05-7.90 (m, 2H), 7.60-7.40 (m, 2H), 7.35-7.05 (m, 10H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.60-5.70 (m, 3H), 4.95-4.50 (m, 5H), 3.70-2.80 (m, 8H). HRMS (calc.): 552.2750 [M <sup>+</sup> - NH <sub>4</sub> ], (found): 552.2746   | 1B   |
| 21  | 28  |    | NH <sub>2</sub>   | 4-[[4-benzyl-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide               | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz), 1.63-1.53 (m, 12H).   | 1A   |
| 22  | 29  |   | NH <sub>2</sub>   | 4-[[4-Amino-6-benzylamino-[1,3,5]triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide                            | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.04 (s, 1H), 7.95 (d, J = 7.3 Hz, 2H), 7.45 (d, J = 7.1 Hz, 2H), 7.38-7.15 (m, 6H), 7.00 (td, J = 8.0 Hz, 1.5 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.67-6.25 (m, 3H), 5.85-5.55 (m, 3H), 4.61 (d, J = 6.3 Hz, 2H), 4.54 (d, J = 5.2 Hz, 2H). HRMS (calc.): 440.2073, (found): 440.2078                                      | 1A   |
| 23  | 30  |  |  | 4-[[6-(2-indanyl-amino)-4-(3-pyridinyl-methyl-amino)-[1,3,5]triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.20-9.00 (m, 1H), 8.70-8.35 (m, 2H), 8.05-7.90 (m, 2H), 7.85-7.55 (m, 1H), 7.55-7.10 (m, 8H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (bd, J = 7.4 Hz, 1H), 6.71 (bt, J = 7.3 Hz, 1H), 6.80-6.00 (m, 3H), 4.84-4.50 (m, 7H), 3.34-3.12 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 539.2546 [M <sup>+</sup> - NH <sub>4</sub> ], (found): 539.2533 | 1B   |





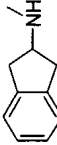

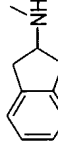
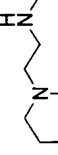
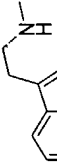
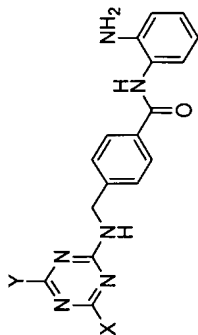
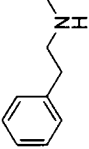


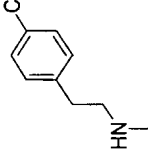

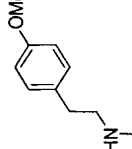

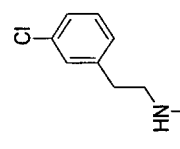
| Ex. | Cpd | Y   | X  | Name  | Characterization  | Schm |
|-----|-----|---|--|---|---|------|
| 24  | 31  |    |   | N-(2-Amino-phenyl)-4-[(4-piperidin-1-yl-6-pyrrolidin-1-yl-[1,3,5]triazin-2-ylamino)-methyl]-benzamide           | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.89 (bs, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.09 (dt, J = 7.7 Hz, 1.6 Hz, 1H), 6.87-6.82 (m, 2H), 4.83 (bs, 1H), 4.62 (d, J = 6.0 Hz, 2H), 4.24 (m, 1H), 3.88 (bs, 1H), 2.04-1.96 (m, 2H), 1.70-1.52 (m, 10H), 1.46-1.38 (m, 2H).           | 1B   |
| 25  | 32  |    |   | N-(2-Amino-phenyl)-4-[(2-piperidin-1-yl-6-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.27 (bs, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.29 (m, 3H), 7.05 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.81-6.76 (m, 2H), 5.62 (bs, 2H), 4.57 (bs, 2H), 3.91 (bs, 2H), 3.69 (m, 4H), 3.45 (m, 2H), 2.57 (t, J = 6.2 Hz, 2H), 2.47 (m, 4H), 1.71 (m, 4H), 1.59-1.50 (m, 6H).                               | 1B   |
| 26  | 33  |    |   | 4-[(6-(2-indanyl-amino)-4-morpholin-4-yl-[1,3,5]triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide         | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.08-7.95 (m, 2H), 7.60-7.43 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.55-6.05 (m, 2H), 4.86-4.60 (m, 5H), 3.80-3.56 (m, 8H), 3.38-3.12 (m, 2H), 3.04-2.82 (m, 2H). | 1B   |
| 27  | 34  |   |  | N-(2-Amino-phenyl)-4-[(2-piperidin-1-yl-6-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.08 (bs, 1H), 8.01 (bd, J = 7.4 Hz, 2H), 7.56-7.43 (m, 2H), 7.33 (bd, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.75 (m, 2H), 4.90-4.58 (m, 5H), 3.66-2.34 (m, 16H).           | 1B   |
| 28  | 35  |  | NH <sub>2</sub>  | 4-[(4-Amino-6-[2-(1H-indol-3-yl)-ethylamino]-[1,3,5]triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide     | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 10.00 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.70-7.50 (m, 1H), 7.50-7.22 (m, 4H), 7.18-6.91 (m, 4H), 6.85 (d, J = 7.1 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.40-5.90 (m, 3H), 4.75-4.50 (m, 2H), 4.37 (s, 2H), 3.62 (d, J = 6.3 Hz, 2H), 2.99 (s, 2H).                         | 1A   |


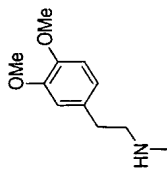

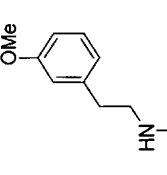

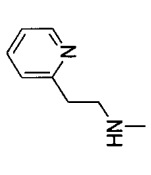

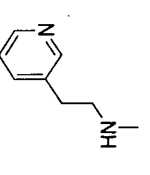
Table 2b

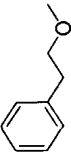

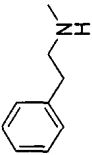

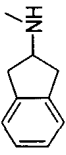



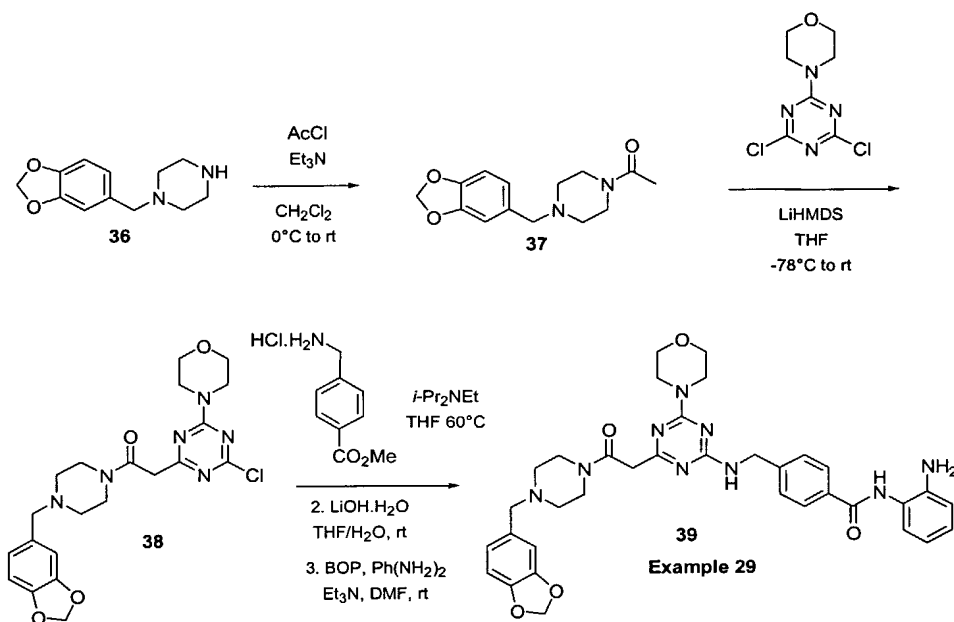
| Ex. | Cpd | X | Y               | Name  | Characterization  | Schm |
|-----|-----|---|-----------------|---|---|------|
| 329 | 470 |   | NH <sub>2</sub> | 4-[(4-amino-6-(3-phenylpropyl-1-amino)-[1,3,5]triazin-2-yl-amino)methyl]-N(2-amino-phenyl)-benzamide            | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.03 (s, 1H), 7.96 (d, J=8.2 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H), 7.35-7.10 (m, 6H), 7.00 (t, J=7.7 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.67 (t, J=7.7 Hz, 1H), 6.60-5.40 (m, 6H), 4.62 (s, 2H), 3.35 (dd, J=12.1, 6.9 Hz, 2H), 2.75-2.60 (m, 2H), 1.95-1.80 (m, 2H).   | 1A   |
| 330 | 471 |   |                 | N(2-amino-phenyl)-4-[(4-cyclopropyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)methyl]-benzamide         | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.04 (s, 1H), 7.96 (d, J=8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.98 (t, J=7.4 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (t, J=7.3 Hz, 1H), 6.20-5.50 (m, 3H), 4.80-4.50 (m, 4H), 3.65-3.45 (m, 2H), 3.00-2.60 (m, 2H), 0.80-0.40 (m, 4H).   | 1B   |
| 331 | 472 |   |                 | N(2-amino-phenyl)-4-[(4-cyclopropyl-methylamino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.06 (bs, 1H), 8.00 (bd, J = 7.1, 2H), 7.50 (bs, 1H), 7.33 (d, J = 6.6 Hz, 1H), 7.28-7.07 (m, 4H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.55-5.70 (m, 3H), 4.90-4.50 (m, 5H), 3.40-2.80 (m, 6H), 1.07 (bs, 1H), 0.44 (bs, 2H), 0.23 (bs, 2H). | 1B   |
| 332 | 473 |   | nBuNH           | N(2-amino-phenyl)-4-[(4-n-butyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)methyl]-benzamide             | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.08 (s, 1H), 7.83 (d, J = 6.6 Hz, 2H), 7.45-7.05 (m, 8H), 7.08 (td, J = 7.8, 1.5 Hz, 1H), 6.84 (t, J = 8.1 Hz, 2H), 6.70-5.00 (m, 3H), 4.70-4.50 (m, 2H), 3.65-3.50 (m, 2H), 3.45-3.25 (m, 2H), 2.40-2.25 (m, 2H), 1.60-1.45 (m, 2H), 1.45-1.00 (m, 2H), 1.00-0.8 (m, 3).                                    | 1B   |



| Ex. | Cpd | X   | Y  | Name  | Characterization   | Schm |
|-----|-----|---|--|---|--|------|
| 333 | 474 |    |   | N-(2-amino-phenyl)-4-({[4-(2-methoxy-ethyl)-1-amino]-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino]-methyl)-benzamide   | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.02 (s, 8.58 (s), 8.40 (dd, J = 7.2, 2 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.51-7.40 (m, 2H), 7.70-6.90 (m, 7H), 6.86 (dd, J = 8.1, 1.2 Hz), 6.76 (dd, J = 7.5, 1.8 Hz), 6.67 (td, J = 7.8, 1.5 Hz), 6.60-5.50 (m, 3H), 4.75-4.55 (m, 4H), 3.65-3.35 (m, 6H), 3.35-3.20 (s, 3H), 2.95-2.75 (m, 2H). | 1B   |
| 334 | 475 |    |   | N-(2-amino-phenyl)-4-({[4-(4-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl)-benzamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.02 (s, 1H), 8.02-7.91 (m, 2H), 7.58-7.40 (m, 2H), 7.28 (s, 4H), 7.20-7.05 (m, 1H), 6.99 (td, J = 7.5, 1.8 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.67 (t, J = 6.9 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.65-3.40 (bs, 2H), 2.95-2.65 (m, 2H), 0.75-0.55 (m, 2H), 0.55-0.40 (m, 2H).         | 1B   |
| 335 | 476 |    |   | N-(2-amino-phenyl)-4-({[6-cyclopropyl-amino-4-(4-methoxy-phenethyl-amino-[1,3,5]triazin-2-yl-amino]-methyl)-benzamide | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.55-7.72 (m, 4H), 7.55-6.75 (m, 9H), 6.75-5.30 (m, 3H), 4.69 (m, 2H), 3.85 (s, 3H), 3.63 (bs, 2H), 2.86 (m, 3H), 0.85 (bs, 2H), 0.61 (bs, 2H).  | 1B   |
| 336 | 477 |  |  | N-(2-amino-phenyl)-4-({[4-(3-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl)-benzamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.03 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.60-7.37 (m, 2H), 7.37-7.12 (m, 5H), 6.99 (t, J = 6.9 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.67-3.45 (m, 2H), 3.00-2.67 (m, 3H), 0.75-0.40 (m, 4H).  | 1B   |

| Ex. | Cpd | X   | Y   | Name   | Characterization   | Schm |
|-----|-----|---|---|--|--|------|
| 337 | 478 |    |    | N-(2-amino-phenyl)-4-({[6-cyclopropyl-amino-4-(3,4-dimethoxy-phenethyl)-amino]-[1,3,5]triazin-2-yl-amino]-methyl})-benzamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.95-6.72 (m, 4H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.20-5.60 (m, 3H), 4.78-4.52 (m, 4H), 3.75 (s, 6H), 3.65-3.42 (m, 2H), 2.95-2.65 (m, 3H), 0.72-0.40 (m, 4H).  | 1B   |
| 338 | 479 |    |    | N-(2-amino-phenyl)-4-({[6-cyclopropyl-amino-4-(3-methoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl})-benzamide      | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.60-7.35 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.99 (td, J = 7.5, 1.5 Hz, 1H), 6.90-6.70 (m, 4H), 6.67 (t, J = 7.8 Hz, 1H), 6.60-5.60 (m, 3H), 4.77-4.50 (m, 4H), 3.76 (s, 3H), 3.65-3.45 (m, 2H), 2.92-2.65 (m, 3H), 0.72-0.42 (m, 4H).  | 1B   |
| 339 | 480 |    |    | N-(2-amino-phenyl)-4-({[6-cyclopropyl-amino-4-(2-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl})-benzamide   | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.03 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.60-7.40 (m, 2H), 7.35-7.08 (m, 3H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.86 (dd, J = 8.1, 1.5 Hz, 1H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.80-3.60 (m, 2H), 3.15-2.90 (m, 2H), 2.90-2.65 (m, 1H), 0.73-0.40 (m, 4H). | 1B   |
| 340 | 481 |  |  | N-(2-amino-phenyl)-4-({[6-cyclopropyl-amino-4-(3-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl})-benzamide   | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.20-9.00 (m, 1H), 8.70-8.50 (m, 2H), 8.00 and 7.88 (2d, J = 7.9 Hz, 2H), 7.75-7.43 (m, 3H), 7.38-6.67 (m, 5H), 6.22-5.78 (m, 3H), 4.80-4.55 (m, 4H), 3.61 (bs, 2H), 3.20-2.65 (m, 3H), 0.80-0.45 (m, 4H).  | 1B   |

| Ex. | Cpd | X   | Y   | Name   | Characterization   | Schm  |
|-----|-----|---|---|--|--|-------|
| 341 | 482 |    |    | N-(2-amino-phenyl)-4-[(4-cyclopropyl-amino-6-phenethoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 9.04 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.35-7.15 (m, 6H), 7.00 (td, J = 7.5, 1.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 7.18-6.35 (m, 2H), 4.75-4.30 (m, 6H), 3.10-2.92 (m, 2H), 0.75-0.63 (m, 2H), 0.57-0.48 (m, 2H).  | 1, 25 |
| 342 | 483 |    | Me  | N-(2-amino-phenyl)-4-[(6-methyl-4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide        | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> + □ DMSO-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.62 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.80-7.44 (m, 3H), 7.40-7.10 (m, 8H), 7.01 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 4.85 (bs, 2H), 4.72-4.54 (m, 2H), 3.63-3.42 (m, 2H), 2.96-2.74 (m, 2H), 2.21 and 2.13 (2s, 3H). | 30    |
| 343 | 484 |    | NH <sub>2</sub>   | N-(2-amino-phenyl)-4-[(4-amino-6-phenyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide                 | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.08 (bs, 1H), 8.48-8.36 (m, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.63-7.42 (m, 5H), 7.33 (d, J = 7.7 Hz, 1H), 7.19 (bs, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.35 and 6.25 (2bs, 2H), 4.87 and 4.75 (2d, J = 5.9 Hz, 2H), 4.65 (bs, 2H).    | 30    |
| 344 | 485 |  |  | N-(2-amino-phenyl)-4-[(6-(2-indanyl-amino)-4-phenyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide     | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): mixture of rotamers, 9.14-8.96 (m, 1H), 8.54-8.30 (m, 2H), 8.09-7.95 (m, 2H), 7.68-7.40 (m, 5H), 7.38-7.08 (m, 6H), 7.03 (t, J = 7.3 Hz, 1H), 6.94-6.76 (m, 2H), 6.71 (t, J = 7.3 Hz, 1H), 5.13-4.54 (m, 5H), 3.49-3.18 (m, 2H), 3.12-2.90 (m, 2H).   | 30    |



### Example 29

**N-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-yl]-2-oxo-ethyl}-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino)-methyl)-benzamide (compound **39**)**

Step 1: N-Acetyl-1-piperonylpiperazine (compound **37**)

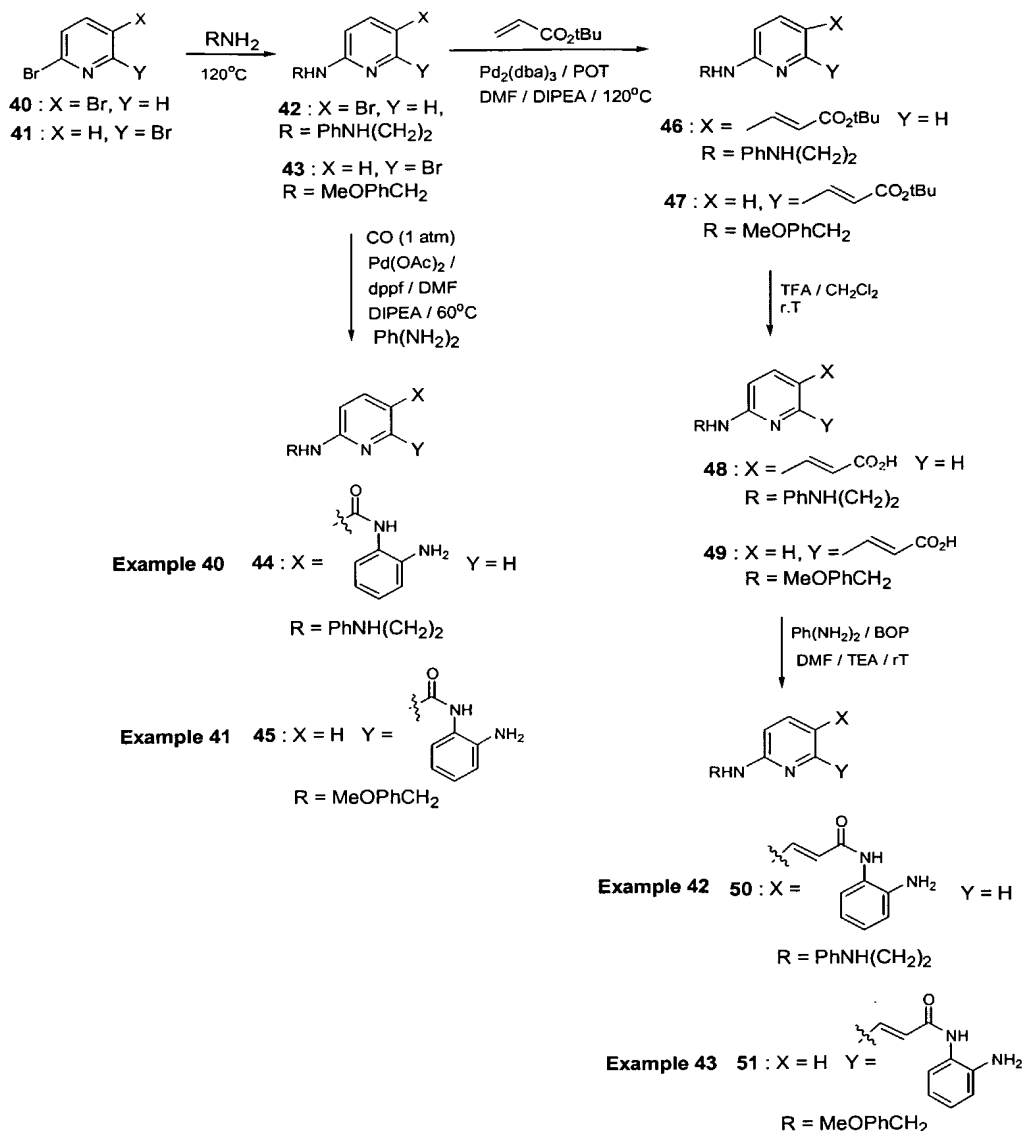
**[0171]** To a stirred solution at 0°C of 1-piperonylpiperazine **36** (5.00 g, 22.7 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added Et<sub>3</sub>N (6.33 mL, 45.4 mmol) followed by acetyl chloride (1.94 mL, 27.2 mmol). The reaction mixture was stirred 30 min. at 0°C and then 2 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub>: 4/96) to afford the title compound **37** (5.52 g, 21.11 mmol, 93% yield) as a yellow solid. <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.83 (s, 1H), 6.72 (m, 2H), 5.92 (s, 2H), 3.59 (t, J = 5.1 Hz, 2H), 3.44-3.40 (m, 4H), 2.42 (dt, J = 5.1 Hz, 5.1 Hz, 4H), 2.06 (s, 3H).

Step 2: 2-Chloro-4-morpholin-4-yl-6-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-[1,3,5]triazine (compound **38**)

**[0172]** To a stirred solution of **37** (3.00 g, 11.4 mmol) in anhydrous THF (25 mL) at  $-78^{\circ}\text{C}$  was slowly added a solution of LiHMDS (11.4 mL, 11.4 mmol, 1 M in THF). The reaction mixture was stirred 1 h at  $-78^{\circ}\text{C}$  and a solution of 2,4-dichloro-6-morpholin-4-yl-[1,3,5]triazine (2.69 g, 11.4 mmol) in anhydrous THF (25 mL) was added. The reaction mixture was slowly warmed up at room temperature and the reaction was quenched after 16 h with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ . The THF was evaporated and the residue was diluted with AcOEt. The organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ( $\text{MeOH}/\text{CH}_2\text{Cl}_2$ : 1/99 $\rightarrow$ 3/97) to afford the title compound **38** (4.84 g, 10.49 mmol, 92% yield) as a pale yellow solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.84 (s, 1H), 6.77-6.69 (m, 2H), 5.95 (s, 2H), 3.75-3.43 (m, 16H), 2.42 (m, 4H).

Step 3: *N*-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound **39**)

**[0173]** The title compound **39** was obtained following the same procedure as Example 1, step 5.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 7.96 (bs, 1H), 7.87 (d,  $J = 8.2$  Hz, 2H), 7.39 (d,  $J = 8.2$  Hz, 2H), 7.33 (d,  $J = 8.5$  Hz, 1H), 7.10 (dt,  $J = 7.6$  Hz, 1.2 Hz, 1H), 6.87-6.81 (m, 3H), 6.75-6.68 (m, 2H), 5.93 (s, 2H), 5.67 (bs, 1H), 4.64 (s, 2H), 3.90 (bs, 2H), 3.75-3.35 (m, 16H), 2.45-2.30 (m, 4H).



### Example 40

#### ***N*-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound 44)**

##### Step 1: *N*-(5-Bromo-pyridin-2-yl)-*N'*-phenyl-ethane-1,2-diamine (compound 42)

**[0174]** A mixture of 2,5-dibromopyridine **40** (2.08 g, 8.6 mmol) and phenyl-1,2-ethyldiamine (1.98 g, 14.6 mmol, 1.7 equiv.) was stirred under nitrogen at 120°C for 6h. After cooling down to room temperature, the solid mixture was ground in a mortar, dissolved in ethyl acetate (200 mL), washed with saturated NaHCO<sub>3</sub> (2 x 50 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. After a quick

purification through a short chromatographic column (silica gel, elution 50% ether in hexanes), a pale yellow solid **42** (1.75 g, 6.01 mmol, 70% yield) was obtained.  $^{13}\text{C}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 158.6, 149.6, 148.8, 139.9, 129.8, 117.1, 113.1, 110.8, 106.6, 43.9, 41.5. LMRS = 294.0 (M+1).

Step 2: *N*-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound **44**)

**[0175]** A mixture of 5-bromo-2-*N*-alkanyl-2-aminopyridine **42** (352 mg, 1.2 mmol), 1,2-phenylenediamine (3.95 mmol, 3.3 equiv.),  $\text{Pd}(\text{OAc})_2$  (0.31 mmol, 26% mol) and 1,1'-bis(diphenylphosphino) ferrocene (124 mg, 0.22 mmol) was suspended in degassed DMF (3mL), treated with diisopropylethyl amine (0.9 mL, 5.2 mmol) and the system flushed with CO. The reaction mixture was warmed up to 60°C and stirred under CO (balloon) for 18 h at this temperature. After evaporation of the DMF under *vacuo*, the residue was purified through a chromatographic column (silica gel, elution 3% to 6% methanol in dichloromethane) to give 258 mg (0.74 mmol, 62 % yield) of the aminoanilide **44**.  $^1\text{H}$ -NMR ( $\text{CD}_3\text{OD}-d_4$ ),  $\delta$  (ppm): 8.67 (d,  $J$  = 2.2 Hz, 1H), 7.97 (dd,  $J$  = 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd,  $J$  = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd,  $J$  = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt,  $J$  = 7.7 Hz, 4.4 Hz, 1H), 6.67 (t,  $J$  = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t,  $J$  = 6.3 Hz, 2H), 3.35 (t,  $J$  = 6.3 Hz, 2H).

### Example 41

***N*-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound **45**)**

Step 1: *N*-(5-Bromo-pyridin-2-yl)-4-methoxybenzylamine (compound **43**)

**[0176]** A mixture of 2,6-dibromopyridine **41** (6.03 mmol, 2 equiv.) and *para*-methoxybenzyl amine (413 mg, 3.01 mmol) was stirred under nitrogen at 120°C for 6h. After identical work-up procedure described before and purification through a pad of silica gel (elution 50% ether in hexanes), a pale yellow solid **43** (773 mg, 2.60 mmol, 87% yield) was obtained.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 159.1, 139.7, 132.1, 130.5, 128.9, 127.2, 116.2, 114.3, 104.8, 55.4, 46.0. LMRS = 295.0 (M+1).

Step 2: *N*-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound **45**)

**[0177]** Following the procedure described in Example 40, step 2, but substituting **43** for **42**, the title compound **45** was obtained in 61% yield.

**Example 42*****N*-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)**

Step 2: 3-[6-(2-Phenylamino-ethylamino)-pyridin-3-yl]-acrylic acid *tert*-butyl ester (compound 46)

**[0178]** In a 50 mL flask, a mixture of **42** (308 mg, 1.05 mmol), *tert*-butylacrylate (0.8 mL, 5.5 mmol), diisopropylethylamine (0.8 mL, 4.6 mmol), tri-*o*-tolylphosphine (POT, 192 mg, 0.63 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (73 mg, 0.08 mmol) in anhydrous DMF (4 mL) was stirred at 120°C (preheated oil bath) for 2h under nitrogen. After DMF removal, the crude residue was submitted to a chromatographic purification (column silica gel, 50% ether in hexanes) to afford 316 mg of **46** (88% yield). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 166.6, 159.3, 149.6, 147.8, 140.7, 134.9, 129.1, 119.8, 117.3, 115.9, 112.6, 107.8, 80.0, 43.5, 40.9, 28.1. LRMS = 340.3 (M+1).

Step 3: 3-[6-(2-Phenylamino-ethylamino)-pyridin-3-yl]-acrylic acid (compound 48)

**[0179]** Ester **46** (0.93 mmol) was dissolved 40 % TFA in dichloromethane (10 mL) and the solution stirred at room temperature overnight. The solvent was removed under *vacuo* distilling with acetonitrile (3x10 mL) and stored under high vacuum for 6h. The solid residue **48** was employed for the next reaction without further purification. LRMS = 284.1 (M+1).

Step 4: *N*-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)

**[0180]** A mixture of acid **48** (0.93 mmol), BOP (495 mg, 1.12 mmol) and 1,2-phenylenediamine (124 mg, 1.15 mmol) were dissolved in dry acetonitrile (4 mL) and treated with triethylamine (0.8 mL, 5.7 mmol). The solution was stirred under nitrogen at room temperature for 16h. After concentration under *vacuo*, the crude was purified through chromatographic column (5% methanol in dichloromethane), then was crystallized from chloroform to give **50** (247 mg, 71% yield). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H).

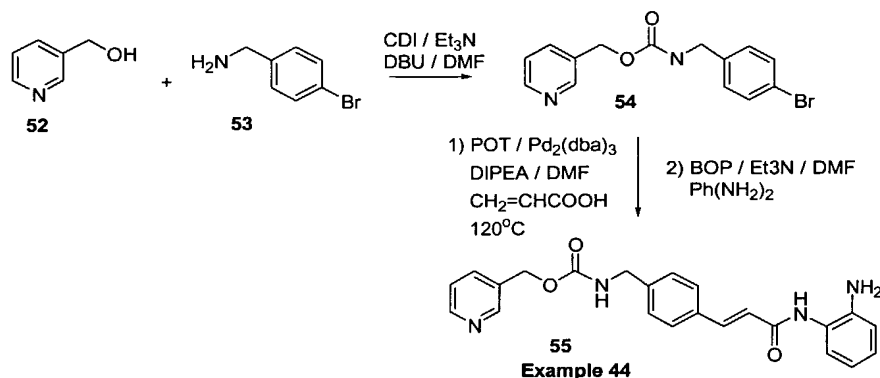


### Example 43

#### ***N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)**

##### Step 2: *N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)

**[0181]** Following the procedure described in Example 42, steps 2, 3, 4, but substituting **43** for **42**, the title compound **51** was obtained in 50% yield (on 2 steps). <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).



### Example 44

#### **4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)**

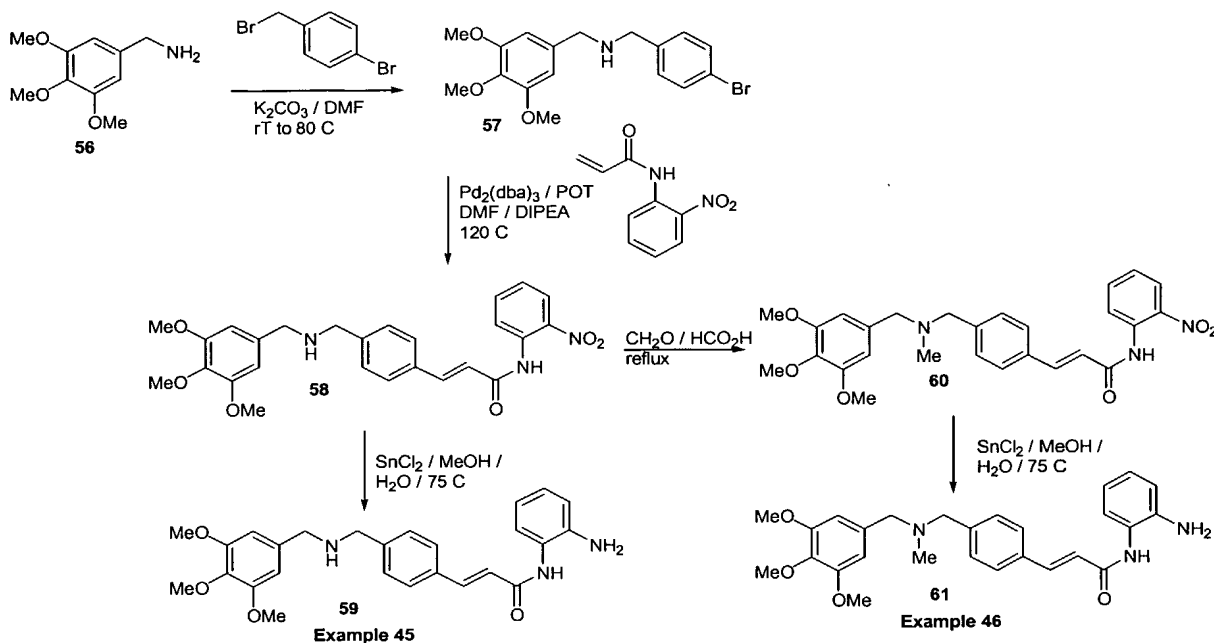
##### Step 1: (4-bromo-benzyl)-carbamic acid pyridin-3-yl-methyl ester (compound 54)

**[0182]** 4-bromobenzylamine HCl (3.0g, 13.4 mmol) was dissolved in DMF (60 mL) at rt and then Et<sub>3</sub>N (4.13 mL, 29.7 mmol) was added dropwise over 10 min to give cloudy solution. To this, DBU (2.42 mL, 16.2 mmol) and 1,1'-carbonyl diimidazole (2.41g, 14.8 mmol) were added. After being stirred for 1 h at rt, 3-pyridylcarbinol (1.44 mL, 14.8 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue obtained was diluted with ether/EtOAc (9:1) and then washed with H<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and then concentrated to give the crude product which was recrystallized from EtOAc to give 2.55g of product **54** (59% yield, LRMS = 323 (M+1)).

Step 2: 4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

**[0183]** Following the procedure described in Example 42, steps 2, 3, but substituting **54** for **42**, and acrylic acid for tert-butyl acrylate the title compound **55** was obtained in an overall yield of 20%.

$^1\text{H}$  NMR: (DMSO- $d_6$ )  $\delta$  (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d,  $J = 3.3$  Hz, 1H), 7.85 (d,  $J = 7.69$  Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d,  $J = 7.69$  Hz, 1H), 6.89 (dd,  $J = 7.14$  Hz,  $J = 7$  Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd,  $J = 7.1$  Hz,  $J = 7$  Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).



**Example 45**

***N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound 59)**

Step 1: (4-Bromo-benzyl)-(3,4,5-trimethoxy-benzyl)-amine (compound 57)

**[0184]** To a stirred suspension of  $\text{K}_2\text{CO}_3$  (522 mg, 3.77 mmol) in dry DMF was added 3,4,5-trimethoxybenzylamine (1.10 mL, 6.44 mmol, 2.2 equiv.) followed by a solution of p-bromobenzylbromide (0.73 g, 2.91 mmol) in dry DMF (8 mL). The mixture was stirred at room temperature under nitrogen for two days in the dark, diluted with dichloromethane (200 mL), washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The crude residue was purified by chromatographic column on silica gel (elution 5% methanol in dichloromethane) to give 2.59 mmol (89% yield) of

dibenzylamine **57**.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 152.5, 138.8, 136.1, 135.4, 130.6, 129.2, 119.8, 104.2, 59.9, 55.3, 52.6, 51.7. LRMS = 368.4 (M+1).

Step 2: *N*-(2-Nitro-phenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound **58**)

Preparation of the nitroacrylanilide

**[0185]** To a mixture of 2-nitroaniline (1.73 g, 12.5 mmol), DMAP (321 mg, 2.6 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (308 mg) in dry dichloromethane (50 mL) at 0°C was added triethylamine (10.6 mL, 76 mmol) followed by acryloylchloride (3.2 mL, 38 mmol, 3.0 equiv.), and the mixture was stirred at room temperature for 16h. The solution was diluted with dichloromethane (250 mL), cooled to 0°C and the excess of reagent quenched with saturated  $\text{NaHCO}_3$  (stirring for 1 h). The organic layer was then washed (5%  $\text{KHSO}_4$ , then brine), dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. After purification through chromatographic column on silica gel (elution 50% ether in hexanes), 642 mg (3.34 mmol, 27% yield) of the amide was obtained.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 163.6, 136.0, 135.6, 134.5, 131.3, 128.6, 125.4, 123.1, 121.8. LRMS = 193.2 (M+1).

Step 3: *N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (**59**)

**[0186]** A mixture of nitro-compound **58** (127 mg, 0.27 mmol),  $\text{SnCl}_2$  (429 mg, 2.26 mmol, 8.4 equiv.) and  $\text{NH}_4\text{OAc}$  (445 mg) was suspended in methanol (9.5 mL) and water (1.5 mL), and the mixture was heated at 70°C for 45 min. The mixture was diluted with ethylacetate (100 mL) and washed with brine and then saturated  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ), filtered, and concentrated. Purification by chromatographic column on silica gel (elution 5 to 10% methanol in dichloromethane) gave 52 mg (43% yield) of **59**.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 8.25 (bs, 1H), 7.59 (d,  $J$  = 15.6 Hz, 1H), 7.38 (d,  $J$  = 7.5 Hz, 2H), 7.29 (d,  $J$  = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t,  $J$  = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d,  $J$  = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).

### Example 46

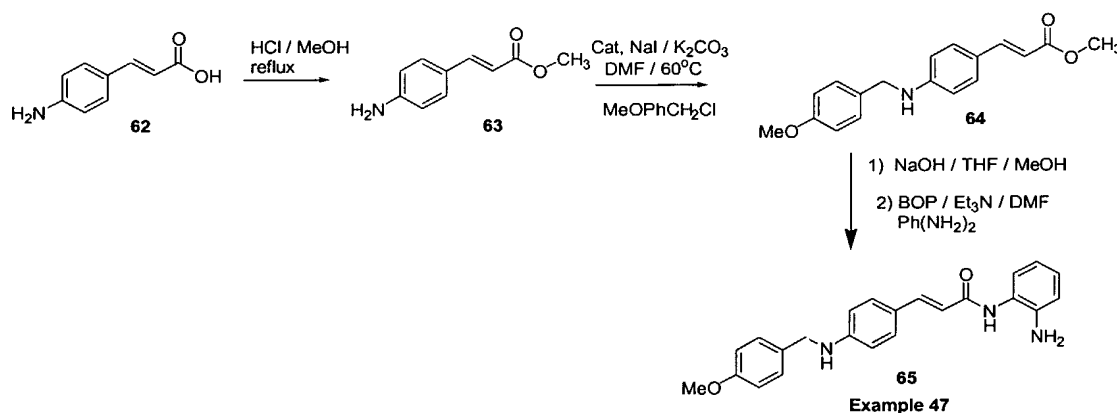
#### ***N*-(2-aminophenyl)-3-(4-[[[(3,4,5-trimethoxy-benzyl)-amino]-methyl]-phenyl]-acrylamide (compound 61)**

Step 1: 3-(4-[[Methyl(3,4,5-trimethoxy-benzyl)-amino]-methyl]-phenyl)-*N*-(2-nitro-phenyl)-acrylamide (compound 60)

**[0187]** Amine **58** (180.2 mg, 0.38 mmol) was dissolved in 88% of HCO<sub>2</sub>H (6 mL), treated with excess of paraformaldehyde (7.67 mmol) and the mixture stirred at 70°C for 2.5h. A saturated NaHCO<sub>3</sub> solution, was added slowly, extracted with dichloromethane (2 x 75 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. After chromatographic column on silica gel (elution 3 to 5% methanol in dichloromethane), pure *N*-methyl amine **60** (118 mg, 63% yield) was obtained. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 164.5, 153.1, 143.5, 142.3, 136.8, 136.1, 136.0, 135.3, 134.9, 132.9, 129.3, 128.2, 125.8, 123.1, 122.2, 120.3, 105.4, 62.2, 61.2, 60.8, 56.0, 42.5. LRMS = 492.5 (M+1).

Step 2: *N*-(2-aminophenyl)-3-(4-[[[(3,4,5-trimethoxy-benzyl)-amino]-methyl]-phenyl]-acrylamide (compound 61)

**[0188]** Following the procedure described in Example 45, step 3, but substituting the nitro-compound **60** for **58**, the title compound **61** was obtained in 72% yield. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H).



### Example 47

#### ***N*-(2-aminophenyl)-3-[4-(4-methoxy-benzylamino)-phenyl]-acrylamide (compound 65)**

##### Step 1: Methyl-3-(4-amino-phenyl)-acrylate hydrochloride (compound 63)

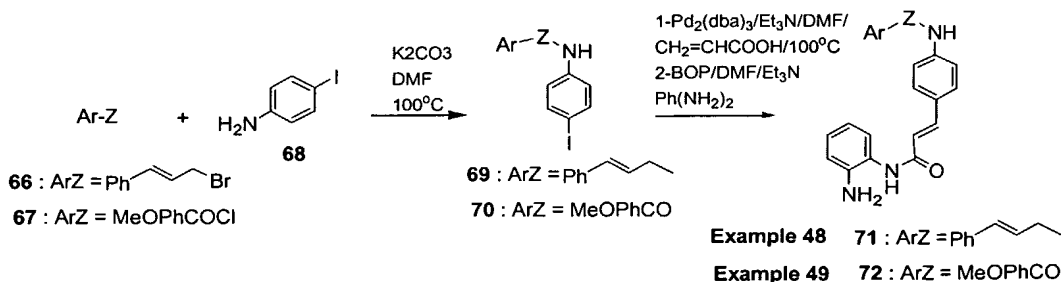
**[0189]** 4-amino-cinnamic acid (10.41 g, 0.052 mol) was dissolved in methanol (100 mL) at rt. A solution of HCl in dioxane (15.6 mL, 4 N) was then added. The reaction mixture was heated at reflux overnight. The clear solution was evaporated to a half volume and then settled down at rt. The white suspension obtained was collected by vacuum filtration. The mother liquid was evaporated again to a quart volume and cooled down to rt. The suspension was filtered again. The combined the solid collected from two filtration was dried *in vacuo* to give 7.16 g of **63** (64.3% yield). LRMS: 178 (M+1).

##### Step 2: Methyl-3-[4-(4-methoxy-benzylamino)-phenyl]-acrylate hydrochloride (compound 64)

**[0190]** To a suspension of compound **63** (3.57 g, 16.7 mmol) in DMF (30 mL) was added Et<sub>3</sub>N. after 10 min 4-methoxybenzyl chloride (2.0 g, 12.8 mmol), NaI (0.38 g, 2.6 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.53 g, 25.5 mmol) were added successively. The mixture was heated at 60°C overnight and evaporated to dryness. The residue was partitioned between NaHCO<sub>3</sub> sat. solution (50 mL) and EtOAc (50mLx3). The combined organic layers were washed with brine and then evaporated to dryness. The residue was purified by flash chromatography and then recrystallized from isopropylalcohol to give 1.16 g **64** (yield 30.6%, LRMS = 298) and 1.46g of **63** (49% recovered yield).

##### Step 3: *N*-(2-aminophenyl)-3-[4-(4-methoxy-benzylamino)-phenyl]-acrylamide (compound 65)

**[0191]** Following the procedure described in Example 42, step 4, but substituting **64** for **48**, the title compound **65** was obtained in 32% yield. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.15 (s, 1H), 7.24–7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).



**Example 48*****N*-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (compound 71)**

Step 1: *N*-(4-Iodo-phenyl)-(3-phenyl-allyl)-amine (compound 69)

**[0192]** Following the procedure described in Example 47, step 2, but substituting **68** for **63**, the title compound **69** was obtained in 70% yield. LRMS = 288 (M+1)

Step 2: *N*-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (**71**)

**[0193]** Following the procedure described in Example 42, steps 2, 4, but substituting **69** for **42**, and acrylic acid for tert-butyl acrylate the title compound **71** was obtained in an overall yield of 60%. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).

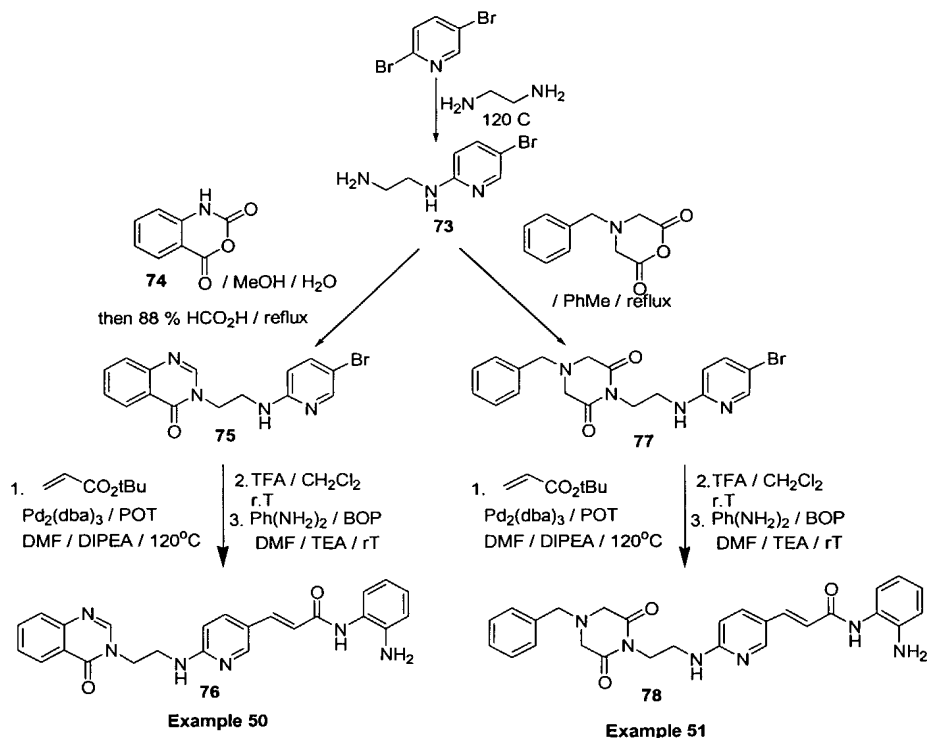
**Example 49*****N*-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)**

Step 1: *N*-(4-Iodo-phenyl)-4-methoxy-benzamide (compound 70)

**[0194]** Following the procedure described in Example 47, step 2, but substituting **68** for **63**, the title compound **70** was obtained in 90% yield. LRMS = 354.0 (M+1)

Step 2: *N*-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

**[0195]** Following the procedure described in Example 42, steps 2, 4, but substituting **70** for **42**, and acrylic acid for tert-butyl acrylate the title compound **72** was obtained in an overall yield of 90%. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).



### Example 50

#### ***N*-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound **76**)**

##### Step 1: *N*-(5-Bromo-pyridin-2-yl)-ethane-1,2-diamine (compound **73**)

**[0196]** Following the procedure described in Example 40, step 1, but using 1,2-diaminoethane as alkyl amine, the title compound **73** was obtained in 84% yield. <sup>13</sup>C NMR (300 MHz, CD<sub>3</sub>OD): 159.1, 148.7, 140.7, 111.7, 107.2, 44.3, 41.7. LRMS = 218.1 (M+1)

##### Step 2: 3-[2-(5-Bromo-pyridin-2-ylamino)-ethyl]-3*H*-quinazolin-4-one (compound **75**)

**[0197]** A suspension of primary amine **73** (1.17 g, 5.40 mmol) and isatoic anhydride **74** (880 mg, 5.40 mmol) in methanol (25 mL) was stirred for 3 h at 50°C and then concentrated. The resulting oily residue was dissolved in 88% formic acid (20 mL) and refluxed overnight. After removal of formic acid, the solid residue was purified through column chromatography on silica gel (5% methanol in dichloromethane) to give 1.24 g (3.6 mmol, 67% yield) of **75**. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): 161.6, 156.8, 147.7, 147.6, 147.2, 139.8, 134.5, 127.4, 126.8, 126.3, 121.6, 110.1, 107.0, 46.3, 40.1. LRMS = 347.1 (M+1).

Step 3: *N*-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound **76**)

**[0198]** Following the procedure described in Example 42, steps 2 to 4, but substituting **75** for **42**, the title compound **76** was obtained in an overall yield of 68 %. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, *J* = 1.9 Hz, 1H), 7.82 (dt, *J* = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.25 (t, *J* = 5.8 Hz, 1H), 6.90 (dt, *J* = 15.7 Hz, 1H), 6.74 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, *J* = 5.2 Hz, 2H), 3.68 (m, *J* = 5.2 Hz, 2H).

**Example 51**

***N*-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound **78**)**

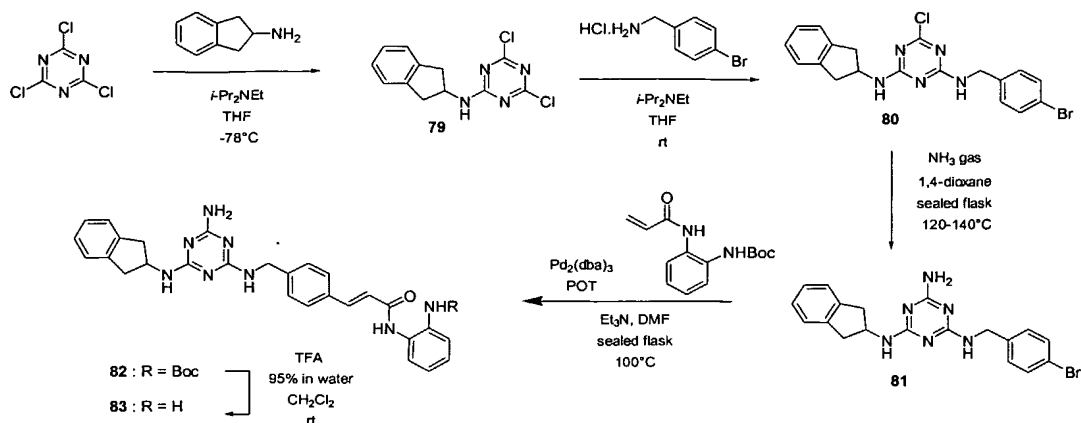
Step 2: 4-Benzyl-1-[2-(5-bromo-pyridin-2-ylamino)-ethyl]-piperazine-2,6-dione (compound **77**)

**[0199]** A suspension of benzyliminodiacetic acid (702 mg, 3.15 mmol) and acetic anhydride (15 mL) was stirred at 120°C for 45 min. The reaction mixture was diluted with dry toluene and concentrated in *vacuo* to remove the volatiles. The residue was dissolved in dry toluene (15 mL) and transferred via cannula to a reaction flask containing the amine **73** (475 mg, 3.2 mmol). The mixture was heated at 90°C for 16 h, concentrated and chromatographed by column on silica gel (elution 5% methanol in dichloromethane) to give 684mg (1.70 mmol, 54% yield) of **77**.

Step 3: *N*-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound **78**)

**[0200]** Following the procedure described in Example 42, steps 2 to 4, but substituting **77** for **42**, the title compound **78** was obtained in an overall yield of 60%. <sup>1</sup>H-NMR (CD<sub>3</sub>OD-*d*<sub>4</sub>), δ (ppm): 8.09 (d, *J* = 1.8 Hz, 1H), 7.68 (dd, *J* = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, *J* = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, *J* = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, *J* = 7.5 Hz, 2H), 3.38 (s, 4H).





Example 52

### Example 52

**(E)-4-[[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl]-N-(2-amino-phenyl)-cinnamide (compound 83)**

#### Step 1: 4,6-Dichloro-2-(2-indanyl-amino)-[1,3,5]triazine (compound 79)

**[0201]** To a stirred solution at  $-78^{\circ}\text{C}$  of cyanuric chloride (13.15 g, 71.33 mmol) in anhydrous THF (100 mL) under nitrogen was slowly cannulated a solution of 2-aminoindan (10.00 g, 75.08 mmol),  $i\text{-Pr}_2\text{NEt}$  (14.39 mL, 82.59 mmol) in anhydrous THF (60 mL). After 50 min, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ $\text{CH}_2\text{Cl}_2$ : 2/98 $\rightarrow$ 5/95) and by co-precipitation (AcOEt/hexanes) to afford the title compound **79** (18.51 g, 65.78 mmol, 92% yield) as a beige powder.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.29-7.18 (m, 4H), 6.02 (bd,  $J = 6.3$  Hz, 1H), 4.94-4.84 (in, 1H), 3.41 (dd,  $J = 16.2, 6.9$  Hz, 2H), 2.89 (dd,  $J = 16.1, 4.5$  Hz, 2H).

#### Step 2: 2-(4-Bromo-benzyl-amino)-4-chloro-6-(2-indanyl-amino)-[1,3,5]triazine (compound 80)

**[0202]** To a stirred solution at room temperature of **79** (2.68 g, 9.52 mmol) in anhydrous THF (50 mL) under nitrogen were added  $i\text{-Pr}_2\text{NEt}$  (4.79 mL, 27.53 mmol) and 4-bromobenzylamine.HCl (2.45 g, 11.01 mmol), respectively. After 17 h, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and

concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH<sub>2</sub>Cl<sub>2</sub>: 3/97→5/95) to afford the title compound **80** (4.00 g, 9.29 mmol, 97% yield) as a white powder. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): mixture of rotamers, 7.52-7.42 (m, 2H), 7.26-7.11 (m, 6H), 6.51 and 6.12 (2 m, 1H), 5.72-5.46 (m, 1H), 4.94-4.64 (m, 1H), 4.62-4.46 (m, 2H), 3.43-3.16 (m, 2H), 2.92-2.74 (m, 2H).

Step 3: 4-Amino-2-(4-bromo-benzyl-amino)-6-(2-indanyl-amino)-[1,3,5]triazine (compound **81**)

**[0203]** In a 75 mL sealed flask, a solution of **80** (2.05 g, 4.76 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH<sub>3</sub> gas for 5 min, and warmed to 140°C for 18 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH<sub>3</sub> gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into 1N HCl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub>: 5/95) to afford the title compound **81** (1.96 g, 4.76 mmol, quantitative yield) as a colorless foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.43 (d, J = 8.2 Hz, 2H), 7.25-7.12 (m, 6H), 5.70-5.10 (m, 2H), 5.00-4.65 (m, 3H), 4.52 (bs, 2H), 3.40-3.10 (m, 2H), 2.90-2.65 (m, 2H).

Step 4: (E)-4-([4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl)-N-[2-(N-t-butoxycarbonyl)-amino-phenyl]-cinamide (compound **82**)

Preparation of N-[2-(N-t-Butoxycarbonyl)-amino-phenyl]-acrylamide

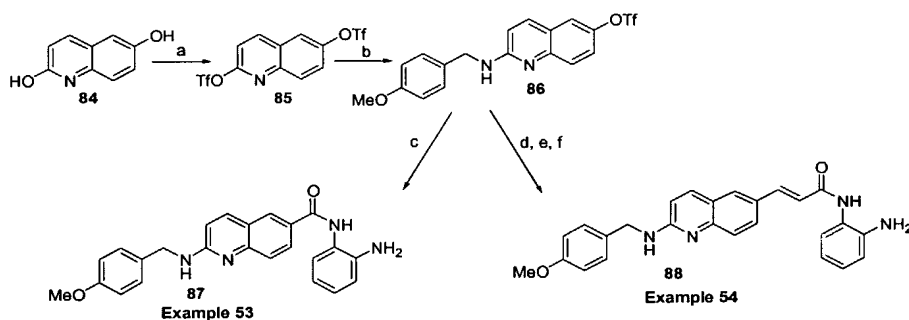
**[0204]** Following the procedure described in Example 45, step 2, but substituting the nitro-compound 2-(N-t-butoxycarbonyl)-amino-aniline for 2-nitroaniline, the title compound was obtained in 77% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.51 (bs, 1H), 7.60-7.45 (m, 1H), 7.38-7.28 (m, 1H), 7.20-7.05 (m, 2H), 6.98 (bs, 1H), 6.41 (dd, J = 17.0 Hz, 1.1 Hz, 1H), 6.25 (dd, J = 16.9 Hz, 10.0 Hz, 1H), 5.76 (dd, J = 10.2 Hz, 1.4 Hz, 1H), 1.52 (s, 9H).

**[0205]** In a 50 mL sealed flask, a solution of **81** (300 mg, 0.73 mmol), the acrylamide (230 mg, 0.88 mmol), Et<sub>3</sub>N (407 μL, 2.92 mmol), tri-*o*-tolylphosphine (POT, 13 mg, 0.04 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (20 mg, 0.02 mmol) in anhydrous DMF (10 mL) was stirred at room temperature, saturated with N<sub>2</sub> gas for 15 min, and warmed to 100°C for 15 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After

separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ( $\text{MeOH}/\text{CH}_2\text{Cl}_2$ : 2/98→5/95) to afford the title compound **82** (240 mg, 0.41 mmol, 56% yield) as a beige solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.46 (bs, 1H), 7.71 (bd,  $J = 15.7$  Hz, 1H), 7.62-7.05 (m, 13H), 6.54 (bd,  $J = 15.9$  Hz, 1H), 5.95-4.90 (m, 4H), 4.85-4.48 (m, 3H), 3.40-3.14 (m, 2H), 2.90-2.70 (m, 2H), 1.52 (s, 9H).

Step 5: (E)-4-[[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl]-N-(2-amino-phenyl)-cinnamide (compound **83**)

**[0206]** To a stirred solution at room temperature of **82** (230 mg, 0.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added TFA (1 mL, 95% in water). After 18 h, the reaction mixture was poured into a saturated aqueous solution of  $\text{NaHCO}_3$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ( $\text{MeOH}/\text{CH}_2\text{Cl}_2$ : 5/95) to afford the title compound **83** (170 mg, 0.35 mmol, 89% yield) as a yellow solid.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 8.87 (bs, 1H), 7.69 (d,  $J = 15.7$  Hz, 1H), 7.59 (bd,  $J = 7.7$  Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd,  $J = 8.0, 1.4$  Hz, 1H), 6.69 (td,  $J = 7.6, 1.4$  Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).



- a.  $\text{Tf}_2\text{O}$  / Py / DMAP / 0 C
- b. p-methoxybenzylamine / 120 C
- c. 1,2-phenylenediamine / CO (40 psi) /  $\text{Pd}(\text{OAc})_2$  / dppf / DMF / DIPEA / 70 C
- d. t Butylacrylate /  $\text{Pd}_2(\text{dba})_3$  / POT / DMF / DIPEA / 120 C
- e. TFA / DCM / rT
- f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

**Example 53*****N*-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)**

Step 1: 2,6-ditrifluoromethanesulfonyloxy-quinoline (compound 85):

[0207] A solution of 2,6-dihydroxyquinoline **84** (1.254 g, 7.78 mmol) and DMAP (a few crystals) in dry pyridine (15 mL) was treated with neat trifluoromethanesulfonic anhydride (5.2 g, 18.4 mmol, 1.2 equiv.) and stirred at 0°C for 5 h. This solution was then poured on a mixture brine/sat NaHCO<sub>3</sub> and extracted with dichloromethane (2 x 150 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by column chromatography on silica gel (30% to 50% ether in hexanes) gave 2.58 g (6.1 mmol, 78% yield) of **85**. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): 154.5, 147.8, 144.6, 142.0, 131.6, 127.8, 124.9, 119.3, 118.7, 114.9. LRMS = 426.0 (M+1).

Step 2: *N*-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)

[0208] Following the procedure described in Example 40, steps 1, 2, but substituting **85** for **40**, the title compound **87** was obtained in 92% yield. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).

**Example 54*****N*-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)**

Step 3: *N*-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

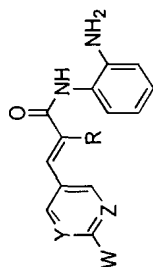
[0209] Following the procedure described in Example 42, steps 1 to 4, but substituting **85** for **40**, the title compound **88** was obtained in an overall yield of 71%. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).

**Examples 55-84**

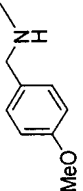
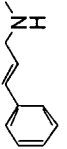
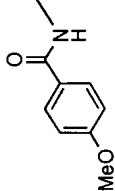
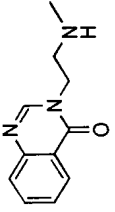
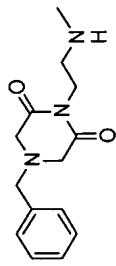
[0210] Examples 55 to 84 describe the preparation of compounds **89** to **118** using the same procedures as described for compounds **44** to **88** in Examples 40 to 54. Characterization data are presented in Tables 3a-d.

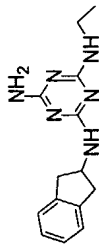
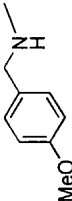
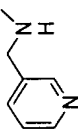
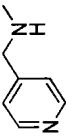
Table 3a

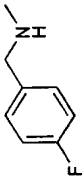
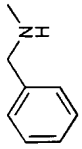

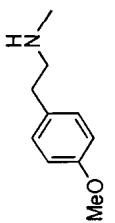
Characterization of Compounds Prepared in Examples 42-84



| Ex. | Cpd. | W | Y  | Z  | R  | Name   | Characterization  | Schm |
|-----|------|---|----|----|----|--|---|------|
| 42  | 50   |   | N  | CH | H  | N-(2-aminophenyl)-3-[6-(2-phenylaminoethylamino)pyridin-3-yl]acrylamide                | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H) | 3    |
| 44  | 55b  |   | CH | CH | H  | {4-[2-(2-amino-phenylcarbamoyl)-vinyl]-phenyl}-carbamic acid pyridin-3-yl methyl ester | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H)   | 4    |
| 45  | 59   |   | CH | CH | H  | N-(2-aminophenyl)-3-[4-{3,4,5-trimethoxybenzylamino)-methyl}-phenyl]-acrylamide        | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H)   | 5    |
| 46  | 61b  |   | N  | CH | Me | N-(2-aminophenyl)-3-[6-(4-methoxybenzylamino)-pyridin-3-yl]-2-methylacrylamide         | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H)  | 3    |

| Ex. | Cpd. | W   | Y  | Z  | R | Name   | Characterization  | Schm |
|-----|------|---|----|----|---|--|---|------|
| 47  | 65   |    | CH | CH | H | N-(2-amino-phenyl)-3-[4-(4-methoxy-benzylamino)-phenyl]-acrylamide                                 | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).  | 6    |
| 48  | 71   |    | CH | CH | H | N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide   | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).  | 7    |
| 49  | 72   |    | CH | CH | H | N-(4-{2-Amino-phenylcarbamoyl}-vinyl)-phenyl-4-methoxy-benzamide                                   | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).  | 7    |
| 50  | 76   |   | N  | CH | H | N-(2-aminophenyl)-3-{6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide          | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).   | 8    |
| 51  | 78   |  | N  | CH | H | N-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide | <sup>1</sup> H-NMR (CD <sub>3</sub> OD-d <sub>4</sub> ), δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H). | 8    |

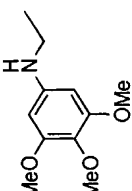
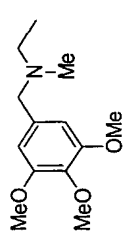
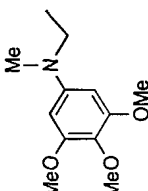
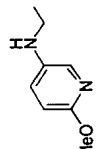
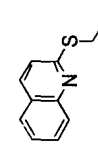
| Ex. | Cpd. | W   | Y  | Z  | R | Name   | Characterization   | Schm |
|-----|------|---|----|----|---|--|--|------|
| 52  | 83   |    | CH | CH | H | (E)-4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino)methyl]-N-(2-amino-phenyl)-cinamide | <sup>1</sup> H NMR (300 MHz, acetone-d <sub>6</sub> ) δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).                               | 9    |
| 55  | 89   |    | N  | CH | H | N-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-3-yl]-acrylamide                          | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.24 (bs, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 5.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.90 (m, 1H), 6.88 (dd, J = 8.5 Hz, 2H), 6.74 (d, J = 6.9 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.45 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H). | 3    |
| 56  | 90   |    | N  | CH | H | N-(2-aminophenyl)-3-[6-[(pyridin-3-ylmethyl)-amino]-pyridin-3-yl]-acrylamide                     | <sup>1</sup> H-NMR (CD <sub>3</sub> OD-d <sub>4</sub> ) δ (ppm): 8.47 (bs, 1H), 8.33 (bs, 1H), 8.02 (m, 1H), 7.73 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.66 (t, J = 7.9 Hz, 1H), 6.53 (m, 2H), 4.54 (m, 2H), 3.59 (bs, 2H).                       | 3    |
| 57  | 91   |  | N  | CH | H | N-(2-aminophenyl)-3-[6-[(pyridin-4-ylmethyl)-amino]-pyridin-3-yl]-acrylamide                     | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.27 (bs, 1H), 8.48 (dd, J = 1.6 Hz, 4.4 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.70 (m, 2H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (m, 3H), 6.90 (t, J = 6.9 Hz, 1H), 6.73 (d, J = 6.9 Hz, 1H), 6.58 (m, 4H), 4.98 (bs, 2H), 4.57 (d, J = 6.0 Hz, 2H).   | 3    |

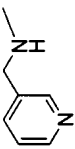

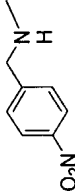
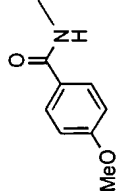
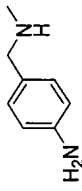
| Ex. | Cpd. | W   | Y | Z  | R | Name  | Characterization   | Schm |
|-----|------|---|---|----|---|---|--|------|
| 58  | 92   |    | N | CH | H | N-(2-aminophenyl)-3-[6-(4-fluorobenzylamino)pyridin-3-yl]acrylamide           | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.24 (bs, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 7.60 (t, J = 5.8 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.36 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.73 (dd, J = 6.9 Hz, 1.0 Hz, 1H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.50 (d, J = 6.0 Hz, 2H).                                   | 3    |
| 59  | 93   |    | N | CH | H | N-(2-aminophenyl)-3-[6-(benzylamino)pyridin-3-yl]acrylamide                   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.24 (bs, 1H), 8.17 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.60 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.89 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.53 (d, J = 6.0 Hz, 2H).                                      | 3    |
| 60  | 94   |    | N | CH | H | N-(2-aminophenyl)-3-[6-(3-phenylpropylamino)pyridin-3-yl]acrylamide           | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.22 (bs, 1H), 8.18 (ds, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.22 (m, 7H), 6.90 (t, J = 7.7 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (m, 3H), 4.92 (bs, 2H), 3.29 (dt, J = 7.7 Hz, 6.0 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.84 (m, J = 7.7 Hz, 2H).   | 3    |
| 61  | 95   |  | N | CH | H | N-(2-aminophenyl)-3-[6-[2-(4-methoxyphenyl)ethylamino]pyridin-3-yl]acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (m, 1H), 6.91 (m, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.57 (m, 3H), 4.92 (bs, 2H), 3.71 (s, 3H), 3.47 (dd, J = 7.3 Hz, 6.0 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H). | 3    |



| Ex. | Cpd. | W | Y | Z  | R | Name  | Characterization   | Schm |
|-----|------|---|---|----|---|---|--|------|
| 62  | 96   |   | N | CH | H | N-(2-aminophenyl)-3-[6-(4-dimethylamino)benzylamino]pyridin-3-yl]acrylamide     | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.23 (bs, 1H), 8.18 (bs, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.41 (m, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H).   | 3    |
| 63  | 97   |   | N | CH | H | N-(2-aminophenyl)-3-[6-(3-imidazol-1-ylpropylamino)pyridin-3-yl]acrylamide      | <sup>1</sup> H-NMR (CD <sub>3</sub> OD-d <sub>4</sub> ), δ (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.98 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). | 3    |
| 64  | 98   |   | N | CH | H | N-(2-aminophenyl)-3-[6-(3-trifluoromethoxybenzylamino)pyridin-3-yl]acrylamide   | <sup>1</sup> H-NMR (acetone-d <sub>6</sub> ), δ (ppm): 8.75 (bs, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 6.83 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (m, 3H), 4.71 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H).  | 3    |
| 65  | 99   |   | N | CH | H | N-(2-aminophenyl)-3-[6-(4-(trifluoromethoxy)benzylamino)pyridin-3-yl]acrylamide | <sup>1</sup> H-NMR (acetone-d <sub>6</sub> ), δ (ppm): 8.81 (bs, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.93 (m, 2H), 6.73 (m, 3H), 4.67 (d, J = 6.0 Hz, 2H), 4.66 (bs, 2H).   | 3    |

| Ex. | Cpd. | W | Y  | Z  | R | Name  | Characterization  | Schm |
|-----|------|---|----|----|---|---|---|------|
| 66  | 100  |   | N  | CH | H | N-(2-aminophenyl)-3-[6-(3,5-difluorobenzylamino)-pyridin-3-yl]-acrylamide                         | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.25 (bs, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.67 (m, 2H), 7.42 (d, J = 15.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.08 (dt, J = 9.3 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 1.9 Hz, 2H), 6.90 (dt, J = 7.3 Hz, 1.4 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.92 (bs, 2H), 4.56 (d, J = 6.0 Hz, 2H). | 3    |
| 67  | 101  |   | N  | CH | H | N-(2-aminophenyl)-3-[6-(3-trifluoromethylbenzylamino)-pyridin-3-yl]-acrylamide                    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.25 (bs, 1H), 8.14 (bs, 1H), 7.86 (m, 6H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.90 (dt, J = 8.8 Hz, 1.1 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.96 (bs, 2H), 4.63 (d, J = 5.8 Hz, 2H).  | 3    |
| 68  | 102  |   | N  | CH | H | 3-[6-(3-aminomethylbenzylamino)-pyridin-3-yl]-N-(2-aminophenyl)-acrylamide                        | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.28 (bs, 1H), 8.17 (bs, 1H), 7.66 (d, J = 5.8 Hz, 2H), 7.37 (m, 6H), 6.88 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.59 (m 3H), 4.55 (d, J = 5.8 Hz, 2H), 3.96 (s, 2H), 3.37 (bs, 4H).   | 3    |
| 70  | 104  |   | CH | CH | H | {4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamoyl acid pyridin-3-yl methyl ester           | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.36 (s, 1H), 8.57 (s, 1H), 8.51 (d, J = 4.6 Hz, 1H), 7.91 (m, 1H), 7.77 (d, J = 7.68 Hz, 1H), 7.28-7.57 (m, 7H), 6.88 (dd, J = 15.66 Hz, 4.4 Hz, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.01 (s, 2H), 4.93 (bs, 2H), 4.10 (d, J = 6.04 Hz, 2H).  | 4    |
| 71  | 105  |   | CH | CH | H | (2-{4-[2-(2-amino-phenylcarbamoyl)-vinyl]-phenyl}-ethyl)-carbamoyl acid pyridin-3-yl methyl ester | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.34 (s, 1H), 8.52 (m, 2H), 7.71 (d, J = 7.69 Hz, 1H), 7.20-7.60 (m, 8H), 6.87 (m, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.03 (s, 2H), 4.92 (s, 2H), 3.30 (m, 2H), 2.75 (m, 2H).   | 4    |

| Ex. | Cpd. | W   | Y  | Z  | R | Name   | Characterization   | Schm |
|-----|------|---|----|----|---|--|--|------|
| 72  | 106  |    | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxyphenylamino)-methyl]-phenyl}-acrylamide   | <sup>1</sup> H-NMR (acetone-d <sub>6</sub> ) δ (ppm): 8.49 (bs, 1H), 8.41 (d, J = 7 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.07 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.76 (m, 1H), 6.74 (m, 1H), 5.99 (s, 2H), 4.36 (s, 2H), 3.69 (s, 6H), 3.68 (bs, 2H), 3.67 (s, 3H).                            | 5    |
| 73  | 107  |    | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxybenzyl)-amino]-methyl}-phenyl}-acrylamide | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ) δ (ppm): 7.70 (bs, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 4.9 Hz, 2H), 7.26 (d, J = 4.9 Hz, 2H), 7.25 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.75 (m, 1H), 6.61 (s, 2H), 6.57 (m, 1H), 4.08 (bs, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.50 (s, 2H), 3.47 (s, 2H), 2.21 (s, 3H). | 5    |
| 74  | 108  |    | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxyphenyl)-amino]-methyl}-phenyl}-acrylamide | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ) δ (ppm): 7.74 (d, J = 15.4 Hz, 1H), 7.50 (d, J = 7.4 Hz, 2H), 7.25 (m, 3H), 7.06 (t, J = 1.9 Hz, 1H), 6.82 (d, J = 7.4 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 5.96 (s, 2H), 4.50 (s, 2H), 3.79 (s, 6H), 3.78 (bs, 2H), 3.77 (s, 3H), 3.00 (s, 3H).  | 5    |
| 75  | 109  |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(6-methoxy-pyridin-3-ylamino)-methyl]-phenyl}-acrylamide  | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.4 (bs, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).  | 5    |
| 76  | 110  |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(quinolin-2-ylsulfanylmethyl)-phenyl]-acrylamide          | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.41 (bs, 1H), 8.21 (d, J = 8.5, 1H), 7.97 (dt, J = 7.7, 8.8 Hz, 2H), 7.78 (dt, J = 7.1 Hz, 8.2 Hz, 1H), 7.61-7.53 (m, 5H), 7.40 (dd, J = 8.5 Hz, 7.6 Hz, 2H), 6.97-6.77 (m, 4H), 6.6 (dt, J = 7.7 Hz, 7.5 Hz, 1H), 4.98 (bs, 2H), 4.65 (bs, 2H).  | 5    |

| Ex. | Cpd. | W   | Y  | Z  | R | Name  | Characterization   | Schm |
|-----|------|---|----|----|---|---|--|------|
| 77  | 111  |    | CH | CH | H | N(2-amino-phenyl)-3-(4-((pyridin-3-ylmethyl)-amino)-phenyl)-acrylamide    | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).   | 6    |
| 78  | 112  |    | N  | CH | H | N(2-Amino-phenyl)-3-(6-styrylamino-pyridin-3-yl)-acrylamide               | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 7.96 (d, J=9.1 Hz, 2H), 7.55 (d, J = 14.2 Hz, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.39-7.29 (m, 4H), 7.07-6.91 (m, 3H), 6.81-6.64 (m, 3H), 6.47-6.38 (m, 1H), 4.21 (bs, 2H).  | 7    |
| 79  | 113  |    | N  | N  | H | N(2-amino-phenyl)-3-[2-(4-nitro-benzylamino)-pyrimidin-5-yl]-acrylamide   | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.30 (s, 1H), 8.58 (bs, 2H), 8.36 (m, 1H), 8.20 (m, 2H), 7.58 (m, 2H), 7.28-7.42 (m, 2H), 6.52 -6.92 (m, 4H), 4.90 (s, 2H), 4.64 (d, J = 6 Hz, 2H).  | 7    |
| 80  | 114  |    | N  | CH | H | N(5-[2-(2-Amino-phenyl)carbamoyl-vinyl]-pyridin-2-yl)-4-methoxy-benzamide | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.87 (bs, 1H), 9.45 (bs, 1H), 8.66 (bs, 1H), 8.33 (d, J = 7.4 Hz, 1H), 8.14-8.08 (m, 3H), 7.63 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 6.8 Hz, 2H), 6.97 (d, J = 12.3 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 5.06 (bs, 2H), 3.88 (s, 3H). | 7    |
| 81  | 115  |  | N  | N  | H | 3-[2-(4-amino-benzylamino)-pyrimidin-5-yl]-N-(2-amino-phenyl)-acrylamide  | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.27 (s, 1H), 8.83 (s, 2H), 7.97 (t, J = 6 Hz, 1H), 7.37 (d, J = 15.9 Hz, 1H), 7.29 (d, J = 7.11 Hz, 1H), 6.96 (d, J = 8.24 Hz, 2H), 6.88 (m, 1H), 6.70 (m, 2H), 6.55 (m, 1H), 6.47 (d, J = 8.2 Hz, 2H), 4.90 (s, 4H), 4.34 (d, J = 6.0 Hz, 2H).   | 7    |

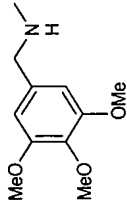
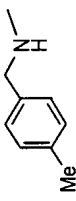
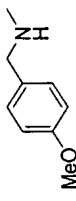
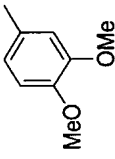
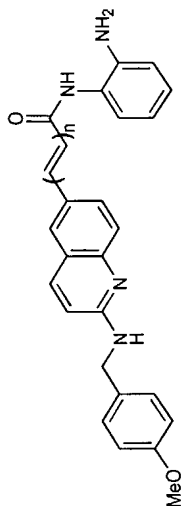
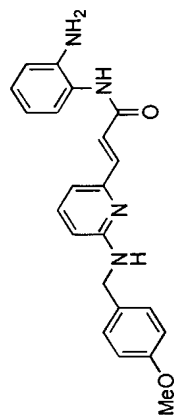
| Ex. | Cpd. | W  | Y | Z  | R | Name  | Characterization  | Schm  |
|-----|------|--|---|----|---|---|---|-------|
| 82  | 116  |   | N | CH | H | N-(2-aminophenyl)-3-[6-(3,4,5-trimethoxybenzylamino)-pyridin-3-yl]-acrylamide | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.38 (bs, 1H), 7.49 (m, 1H), 7.42 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.41 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.10 (bs, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.0 Hz, 1H), 6.73 (m, 1H), 6.65 (m, 2H), 6.36 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 15.0 Hz, 1H), 4.34 (s, 2H and bs, 2H), 3.84 (s, 3H), 3.81 (s, 6H). | 7, 3  |
| 83  | 117  |   | N | CH | H | N-(2-Amino-phenyl)-3-[6-(4-methylbenzylamino)-pyridin-3-yl]-acrylamide        | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 8.28 (bs, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.08 (dt, J = 8.2 Hz, 7.7 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 6.87 (t, J = 8.2 Hz, 1H), 6.75 (d, J = 15.1 Hz, 1H), 4.57 (s, 2H), 2.53 (s, 3H).                 | 7     |
| 84  | 118  |   | N | N  | H | N-(2-amino-phenyl)-3-[2-(4-methoxybenzylamino)-pyrimidin-5-yl]-acrylamide     | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.27 (s, 1H), 8.54 (s, 2H), 8.12 (m, 1H), 7.30 (m, 4H), 6.53-6.91 (m, 6H), 4.90 (s, 2H), 4.46 (d, J = 4.9 Hz, 2H), 3.7 (s, 3H).   | 7     |
| 84b | 118b |  | N | CH | H | N-(2-Amino-phenyl)-3-[6-(3,4-dimethoxyphenyl)-pyridin-3-yl]-acrylamide        | <sup>1</sup> H NMR (20% CD <sub>3</sub> OD in CDCl <sub>3</sub> ): δ (ppm): 8.75 (s, 1H), 7.95 (m, 1H), 7.74-7.59 (m, 3H), 7.50 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.07 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.89-6.83 (m, 3H), 3.96 (s, 3H), 3.91 (s, 3H).   | 9, 15 |

Table 3b



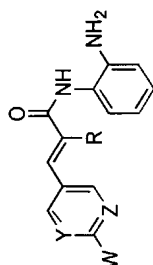
| Ex. | Cpd. | n | Name   | Characterization  | Scheme |
|-----|------|---|--|---|--------|
| 53  | 87   | 0 | 2-(4-methoxybenzylamino)-quinoline-6-carboxylic acid (2-aminophenyl)-amide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs, 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H). | 10     |
| 54  | 88   | 1 | N-(2-aminophenyl)-3-[2-(4-methoxybenzylamino)-quinolin-6-yl]-acrylamide    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).                             | 10     |

Table 3c



| Ex. | Cpd. | Name   | Characterization  | Scheme |
|-----|------|--|---|--------|
| 43  | 51   | N-(2-aminophenyl)-3-[6-(4-methoxybenzylamino)-pyridin-2-yl]-acrylamide | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H). | 3      |

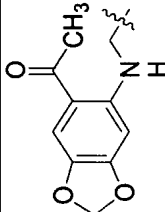
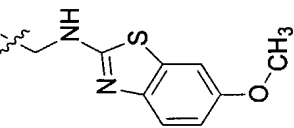
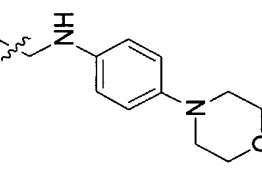
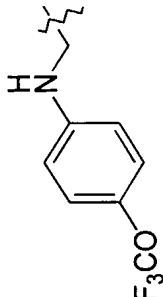
Table 3d

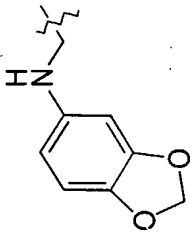
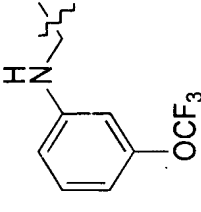
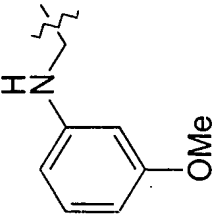
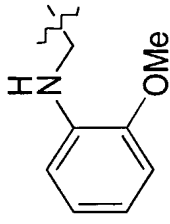
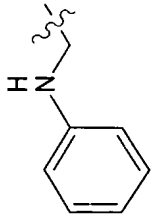


| Ex. Cpd | W | Y  | Z  | R | Name  | Characterization  | Schm        |
|---------|---|----|----|---|---|---|-------------|
| 347 492 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(4,6-dimethoxy-<br>pyrimidin-2-ylamino)-<br>methyl]-phenyl}-<br>acrylamide      | <b><sup>1</sup>H-NMR (DMSO-d6)</b> , δ (ppm): 9.36 (bs, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.48 (s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 6.91 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 7.4, 7.7 Hz, 1H), 5.35 (s, 1H), 4.93 (bs, 2H), 4.46 (dd, J = 6.04 Hz, 3.32 (s, 6H) | <b>3, 7</b> |
| 348 493 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(4-chloro-6-<br>methoxy-pyrimidin-2-<br>ylamino)-methyl]-<br>phenyl}-acrylamide | <b><sup>1</sup>H-NMR (DMSO-d6)</b> , δ (ppm): 9.37 (bs, 1H), 7.58-7.50 (m, 3H), 7.37-7.32 (m, 3H), 6.94-6.83 (m, 2H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.5, 1H), 6.13 (bs, 1H), 4.94 (bs, 2H), 4.48 (d, J = 6.0, 2H), 3.84 (s, 3H)  | <b>3, 7</b> |
| 349 494 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-(3,5-dimethoxy-<br>benzylamino)-phenyl}-<br>acrylamide                           | <b><sup>1</sup>H-NMR (DMSO-d6)</b> , δ (ppm): 9.38 (bs, 1H), 7.55-7.40 (m, 6H), 6.88-6.57 (m, 3H), 6.35-6.32 (m, 1H), 5.73 (m, 3H), 4.94 (s, 2H), 4.26 (s, 2H), 3.63 (s, 6H).   | <b>3, 7</b> |
| 350 495 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-(3,5-dinitro-<br>benzylamino)-phenyl}-<br>acrylamide                             | <b><sup>1</sup>H-NMR (DMSO-d6)</b> , δ (ppm): 9.38 (bs, 1H), 7.74 (bs, 3H), 7.61 (d, J = 8.2 Hz, 2H), 7.56-7.44 (m, 3H), 7.32 (d, J = 8.0 Hz, 1H), 6.91-6.85 (m, 2H), 6.73 (d, J = 7.9 Hz, 1H), 6.66-6.56 (m, 1H), 4.93 (bs, 2H), 4.52 (bs, 2H).  | <b>3, 7</b> |

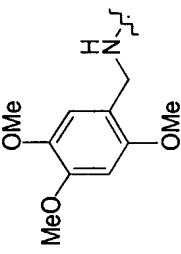
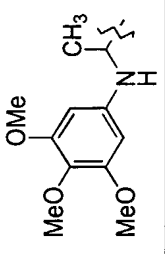
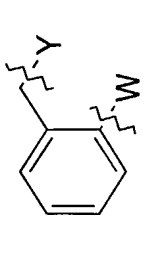
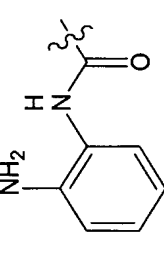
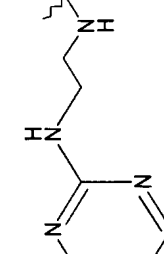
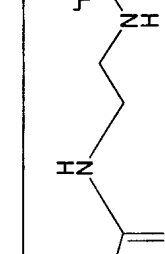
| Ex. | Cpd | W | Y  | Z  | R | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|---|--|------|
| 351 | 496 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(3-trifluoromethoxy-phenylamino-phenyl)-acrylamide                                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.22 (bs, 1H), 7.52 (d, J=7.9 Hz, 2H), 7.44 (bs, 1H), 7.38 (bs, 3H), 7.28 (d, J=6.9 Hz, 2H), 6.95-6.92 (m, 2H), 6.79 (d, J=8.2 Hz, 1H), 6.69-6.59 (m, 3H), 4.95 (bs, 2H), 4.45 (bs, 2H).   | 58   |
| 352 | 497 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxyphenoxymethyl)-phenyl]-acrylamide                                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.45 (bs, 1H), 8.01 (bs, 2H), 7.78-7.5 (m, 4H), 7.49-7.40 (m, 1H), 6.98 (dd, J=7.0, 8.2 Hz, 1H), 6.82 (d, J=7.0 Hz, 1H), 6.64 (dd, J=7.0, 7.6 Hz, 1H), 6.41 (bs, 2H), 5.17 (s, 2H), 3.81 (s, 6H), 3.64 (s, 3H).  | 3, 7 |
| 353 | 498 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-acrylamide                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.22 (bs, 1H), 7.17 (d, J=8.2 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.93 (d, J=7.6 Hz, 1H), 6.85 (bs, 1H), 6.77 (bs, 1H), 6.60-6.53 (m, 3H), 6.43-6.40 (m, 2H), 4.97 (bs, 2H), 4.43 (bs, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.87-2.85 (m, 2H), 2.65-2.62 (m, 2H).   | 37   |
| 354 | 499 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(((1H-indol-2-ylmethyl)(3,4,5-trimethoxy-phenyl)-amino)-methyl)-phenyl]-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 10.77 (bs, 1H), 9.39 (bs, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.7 Hz, 2H), 7.37 (d, J=7.9 Hz, 2H), 7.26 (d, J=7.9 Hz, 2H), 7.10 (t, J=7.5 Hz, 2H), 7.00-6.83 (m, 4H), 6.78 (d, J=7.9 Hz, 1H), 6.61 (t, J=7.5 Hz, 1H), 5.98 (s, 1H), 5.32 (bs, 1H), 4.98 (bs, 2H), 4.32 (d, J=5.2 Hz, 2H), 3.98 (bs, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H). | 58   |
| 355 | 500 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxyphenylsulfanylmethyl)-phenyl]-acrylamide                          | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.69 (bs, 1H), 8.04 (d, J=8.3 Hz, 2H), 7.78 (d, J=8.3 Hz, 2H), 7.58-7.55 (m, 2H), 7.06 (d, J=6.2 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 6.90 (d, J=7.0 Hz, 1H), 6.60 (bs, 1H), 5.81 (s, 2H), 4.34 (bs, 2H), 3.78 (s, 6H), 3.67 (s, 3H).  | 3, 7 |



| Ex. | Cpd | W   | Y  | Z  | R | Name  | Characterization   | Schm  |
|-----|-----|---|----|----|---|---|--|-------|
| 356 | 501 |    | CH | CH | H | 3-[4-{(6-Acetyl-benzo[1,3]dioxol-5-ylamino-methyl)-phenyl}-N(2-amino-phenyl)-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.81 (bs, 1H), 7.95 (d, J=7.9 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4 Hz, 1H), 7.02-7.00 (m, 2H), 6.85 (d, J=7.5 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.60 (bs, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.60 (bs, 2H), 2.50 (bs, 3H).                   | 58    |
| 357 | 502 |    | CH | CH | H | N(2-Amino-phenyl)-3-[4-{(5-methoxy-benzothiazol-2-ylamino-methyl)-phenyl}-acrylamide    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.43 (bs, 1H), 8.37 (bs, 1H), 7.66-7.57 (m, 3H), 7.49 (d, J=7.5 Hz, 2H), 7.37-7.33 (m, 3H), 6.96-6.90 (m, 1H), 6.87 (d, J=8.8 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.63 (t, J=7.5 Hz, 1H), 4.99 (bs, 2H), 4.64 (bs, 2H), 3.37 (s, 3H).   | 58    |
| 358 | 503 |    | CH | CH | H | N(2-Amino-phenyl)-3-[4-{(4-morpholin-4-yl-phenylamino)-methyl)-phenyl}-acrylamide       | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (bs, 1H), 7.63-7.56 (m, 3H), 7.47 (d, J=7.9 Hz, 2H), 7.39 (d, J=7.5 Hz, 1H), 6.95 (d, J=8.3 Hz, 1H), 6.82 (bs, 1H), 6.77 (d, J=8.4 Hz, 2H), 6.66-6.56 (m, 3H), 5.91 (bs, 1H), 5.01 (bs, 2H), 4.30 (bs, 2H), 3.74 (bs, 4H), 2.93 (bs, 4H).                                 | 58    |
| 359 | 504 |  | CH | CH | H | N(2-Amino-phenyl)-3-[4-{(4-trifluoromethoxy-phenylamino)-methyl)-phenyl}-acrylamide     | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.64 (d, J=7.9 Hz, 2H), 7.59 (d, J=15.9 Hz, 1H), 7.48 (d, J=8.0 Hz, 2H), 7.39 (d, J=7.4 Hz, 1H), 7.10 (d, J=8.2 Hz, 2H), 6.99 (d, J=7.1 Hz, 1H), 6.92 (d, J=15.4 Hz, 1H), 6.81 (dd, J=1.3, 8.0 Hz, 1H), 6.61-6.68 (m, 4H), 4.99 (s, 2H), 4.36 (d, J=6.0 Hz, 2H). | 3, 33 |

| Ex. | Cpd | W   | Y  | Z  | R | Name  | Characterization  | Schm  |
|-----|-----|---|----|----|---|---|---|-------|
| 360 | 505 |    | CH | CH | H | N-(2-Amino-phenyl)-3-<br>[4-(benzo[1,3]dioxol-5-<br>ylamino)methyl]-<br>phenyl]-acrylamide          | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 1.4, 7.7 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.05 (m, 2H), 5.87 (s, 2H), 4.99 (s, 2H), 4.29 (d, J = 6.0 Hz, 2H). | 3, 33 |
| 361 | 506 |    | CH | CH | H | N-(2-Amino-phenyl)-3-<br>[4-((3-<br>trifluoromethoxy-<br>phenylamino)methyl)-<br>phenyl]-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 8.2, 8.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 15.2 Hz, 1H), 6.81 (m, 2H), 6.64 (m, 2H), 6.49-6.55 (m, 2H), 5.00 (s, 2H), 4.38 (d, J = 5.3 Hz, 2H).  | 3, 33 |
| 362 | 507 |    | CH | CH | H | N-(2-Amino-phenyl)-3-<br>[4-((3-methoxy-<br>phenylamino)methyl)-<br>phenyl]-acrylamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.90-7.02 (m, 3H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.0 Hz, 1H), 6.36 (m, 1H), 6.24 (d, J = 8.2 Hz, 1H), 6.18 (m, 2H), 5.00 (s, 2H), 4.34 (d, J = 5.3 Hz, 2H), 3.69 (s, 3H).   | 3, 33 |
| 363 | 508 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>[4-((2-methoxy-<br>phenylamino)methyl)-<br>phenyl]-acrylamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.58 (d, J = 15.2 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.0 Hz, 1H), 6.94-7.00 (m, 1H), 6.87 (d, J = 7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 7.6, 7.6 Hz, 1H), 6.56-6.66 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.68 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.41 (d, J = 6.4 Hz, 2H), 3.87 (s, 3H).          | 3, 33 |
| 364 | 509 |  | CH | CH | H | N-(2-Amino-phenyl)-3-<br>[4-phenylaminomethyl-<br>phenyl]-acrylamide                                | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.10 (2d, J = 7.5, 7.5 Hz, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.55-6.64 (m, 4H), 6.32 (t, J = 6.0, 1H), 4.99 (s, 2H), 4.35 (d, J = 5.7 Hz, 2H).   | 3, 33 |

| Ex. | Cpd | W   | Y  | Z  | R  | Name   | Characterization  | Schm  |
|-----|-----|-----|----|----|----|--|---|-------|
| 365 | 510 |     | CH | CH | H  | N-(2-Amino-phenyl)-3-{4-[(4-isopropyl-phenylamino)-methyl]-phenyl}-acrylamide  | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.89-6.99 (m, 4H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.6 Hz, 1H), 6.56 (d, J = 8.2 Hz, 2H), 6.14 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 2.76 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H).   | 3, 33 |
| 366 | 511 |     | CH | CH | H  | N-(2-Amino-phenyl)-3-[4-(biphenyl-4-ylaminomethyl)-phenyl]-acrylamide  | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 5H), 7.40-7.52 (m, 7H), 7.27 (dd, J = 7.0, 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 15.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 2H), 6.64 (dd, J = 7.6 Hz, 1H), 6.56 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.12 (d, J = 5.9 Hz, 2H).   | 3, 33 |
| 367 | 512 |     | CH | N  | H  | N-(2-Amino-phenyl)-3-{6-[(3,4,5-trimethoxy-phenylamino)-methyl]-pyridin-3-yl}-acrylamide                                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.50 (s, 1H), 8.81 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 15.7 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 6.96-7.05 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.26 (m, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 6H), 3.56 (s, 3H).   | 3, 33 |
| 369 | 514 |     | CH | CH | H  | N-(2-Amino-phenyl)-3-{4-[(1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-ethylamino)-methyl]-phenyl}-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.50 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.81-7.72 (s, 3H), 7.66 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.45-7.26 (m, 4H), 7.24-7.15 (m, 2H), 7.00-6.86 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 7.5 Hz, 1H), 5.45 (d, J = 16.8 Hz, 1H), 5.33 (d, J = 16.8 Hz, 1H), 4.62 (bs, 1H), 4.25 (d, J = 12.9 Hz, 1H), 4.92 (d, J = 12.9 Hz, 1H), 1.91 (m, 2H), 1.28 (m, 1H), 0.90 (m, 1H), 0.72 (t, J = 7.5 Hz, 3H). | 55    |
| 371 | 516 | Br- | CH | CH | CH | N-(2-Amino-phenyl)-3-(4-bromo-phenyl)-acrylamide   | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 9.47 (bs, 1H), 7.72-7.56 (m, 5H), 7.39 (d, J = 7.4 Hz, 1H), 7.00-6.95 (m, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.64 (t, J = 7.1 Hz, 1H), 5.00 (bs, 2H).  | 14    |

| Ex. Cpd | W   | Y  | Z  | R  | Name  | Characterization   | Schm     |
|---------|---|----|----|----|---|--|----------|
| 372 517 |    | CH | CH | CH | N(2-Amino-phenyl)-4-(2,4,5-trimethoxybenzylamino)-benzamide                       | <sup>1</sup> H NMR: (CD <sub>3</sub> OD) δ (ppm): 7.61 (d, J=15.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.25 (d, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.81 (t, J=7.0 Hz, 1H), 6.76 (s, 1H), 6.70 (d, J=8.4 Hz, 2H), 6.92 (d, J=15.4 Hz, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.77 (s, 3H).                | 1, 7, 10 |
| 373 518 |    | CH | CH | CH | N(2-Amino-phenyl)-3-{4-[1,3,4,5-tetramethoxyphenylamino]ethyl}phenylacrylamide    | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.24 (s, 1H), 8.00 (d, J=12Hz, 1H), 7.80 (d, J=12Hz, 1H), 7.40-7.70 (m, 7H), 6.80-7.00 (m, 2H), 6.70 (d, J=12Hz, 1H), 6.20 (s, 2H), 4.50 (m, 1H), 3.70 (s, 6H), 3.50 (s, 3H), 1.50 (d, 3H).   | 58       |
| 374 519 |    | C  | CH | H  | N(2-Amino-phenyl)-3-(9H-fluorenyl)acrylamide                                      | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.41 (s, 1H), 8.00 (t, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.77-7.56 (m, 3H), 7.52-7.32 (m, 3H), 7.00 (d, J = 15.8 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 5.00 (s, 2H), 4.03 (s, 2H).   | 59       |
| 375 520 |    | CH | CH | H  | N(2-Amino-phenyl)-4-[2-amino-phenylcarbamoyl]vinylbenzamide                       | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 9.43 (s, 1H), AB system (δ <sub>A</sub> = 8.05, δ <sub>B</sub> = 7.75, J = 7.9 Hz, 4H), 7.62 (d, J = 15.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.05-6.88 (m, 3H), 6.78 (t, J = 7.9 Hz, 2H), 6.65-6.55 (m, 2H), 4.96 and 4.92 (2s, 4H).               | 59       |
| 376 521 |   | N  | CH | H  | N(2-Amino-phenyl)-3-{6-[2-(pyrimidin-2-ylamino)ethylamino]pyridin-3-yl}acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.29 (s, 1H), 8.32 (d, J = 4.9 Hz, 2H), 8.24 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.48 (d, J = 15.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.26 (bs, 2H), 6.96 (t, J = 6.9 Hz, 1H), 6.80 (dd, J = 1.1, 7.7 Hz, 1H), 6.69-6.61 (m, 4H), 5.00 (s, 2H), 3.52 (bs, 4H).                  | 3        |
| 377 522 |  | N  | CH | H  | N(2-Amino-phenyl)-3-{6-[2-(thiazol-2-ylamino)ethylamino]pyridin-3-yl}acrylamide   | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD) δ (ppm): 8.12 (s, 1H), 8.08 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 15.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 15.4 Hz, 1H), 6.65 (s, 1H), 4.90 (s, 5H), 3.50-3.45 (m, 4H), 3.30 (d, J = 1.3 Hz, 1H). | 3        |

| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization  | Schm      |
|---------|---|----|----|---|--|---|-----------|
| 378 523 |   | CH | CH | H | N(2-Amino-phenyl)-3-(4-[(2-morpholin-4-ylethyl){3,4,5-trimethoxy-phenyl}-amino]-methyl)-phenyl)-acrylamide | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.83 (d, J = 15.6 Hz, 1H), 7.67 (d, J = 7.8 Hz, 2H), 7.62-7.58 (m, 2H), 7.53-7.51 (m, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 15.6 Hz, 1H), 4.99 (bs, 9H), 4.84 (bs, 2H), 4.22 (t, J = 6.5 Hz, 2H), 4.05 (s, 4H), 3.85 (s, 6H), 3.76 (s, 3H), 3.57-3.50 (m, 4H).      | 3, 33, 57 |
| 379 524 |   | N  | CH | H | N(2-Amino-phenyl)-3-[6-(3-hydroxy-benzylamino)-pyridin-3-yl]-acrylamide                                    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.32 (s, 1H), 9.26 (s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.7 Hz), 7.10 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.75 (m, 3H), 6.59 (m, 4H), 4.98 (bs, 2H), 4.46 (d, J = 5.8 Hz, 2H). | 3         |
| 380 525 |   | N  | CH | H | N(2-Amino-phenyl)-3-[6-[3-(2,2,2-trifluoroethoxy)-benzylamino]-pyridin-3-yl]-acrylamide                    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.25 (s, 1H), 8.18 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.30 (m, 2H), 7.00 (m, 2H), 6.92 (m, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.60 (m, 3H), 4.92 (s, 2H), 4.73 (q, J = 8.8 Hz, 2H), 4.52 (d, J = 5.8 Hz, 2H).          | 3         |
| 381 526 |   | CH | CH | H | N(2-Amino-phenyl)-3-(4-[(3-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino)-methyl]-phenyl)-acrylamide     | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.64 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.49 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.21 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.88-6.71 (m, 4H), 4.88 (bs, 4H), 4.34 (s, 2H), 2.86 (t, J = 4.1 Hz, 4H), 2.67 (bs, 4H), 2.41 (s, 3H).                               | 3, 33, 58 |
| 382 527 |   | CH | CH | H | N(2-Amino-phenyl)-3-(4-[(3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino)-methyl]-phenyl)-acrylamide      | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.43 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.00-6.88 (m, 2H), 6.85-6.79 (m, 2H), 6.63 (t, J = 7.6 Hz, 1H), 6.44-6.30 (m, 3H), 4.99 (bs, 2H), 4.30 (d, J = 5.5 Hz, 2H), 2.87 (bs, 4H), 2.55 (m, 4H), 2.27 (s, 3H).      | 3, 33, 58 |
| 383 528 |   | CH | CH | H | N(2-Amino-phenyl)-3-[4-(3-hydroxy-phenylamino)-methyl]-phenyl)-acrylamide                                  | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 7.49 (d, J = 14.0 Hz, 1H); 7.32 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.05 (m, 1H), 6.96 (m, 1H), 6.90 (m, 3H), 6.76 (m, 1H), 6.55 (d, J = 14.0 Hz, 1H), 6.03 (m, 1H), 5.99 (m, 1H), 4.30 (bs, 5H), 4.10 (s, 2H).  | 3, 33     |

| Ex. | Cpd | W | Y  | Z  | R | Name   | Characterization   | Schm  |
|-----|-----|---|----|----|---|--|--|-------|
| 384 | 529 |   | CH | CH | H | N{(2-Amino-phenyl)-3-[4-[(4-trifluoromethyl)-pyrimidin-2-ylamino)-methyl]-phenyl)-acrylamide | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.73 (d, J = 16.0 Hz, 1H); 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.03 (dt, J = 7.7, 1.4 Hz, 1H), 6.89 (d, J = 1.1 Hz, 1H), 6.85 (m, 1H), 6.73 (dt, J = 7.7, 1.1 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H), 4.87 (bs, 2H), 4.62 (s, 2H).   | 3, 33 |
| 385 | 530 |   | CH | CH | H | N{(2-Amino-phenyl)-3-[4-[(3-hydroxymethyl)-phenylamino)-methyl]-phenyl)-acrylamide           | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.90 (s, 1H), 7.58 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H); 7.37 (d, J = 8.0 Hz, 1H), 7.11 (m, 1H), 7.00 (m, 3H), 6.85 (d, J = 15.4 Hz, 1H), 6.63 (s, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.7 Hz, 1H), 4.35 (s, 2H), 4.32 (s, 2H).   | 3, 33 |
| 386 | 531 |   | CH | CH | H | N{(2-Amino-phenyl)-3-[4-[(4-pyridin-4-ylmethyl)-phenylamino)-methyl]-phenyl)-acrylamide      | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (s, 1H), 8.46 (d, J = 4.7 Hz, 2H); 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 15.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4.7 Hz, 2H), 7.00 (d, J = 15.7 Hz, 1H), 6.92 (d, J = 6.9 Hz, 2H), 6.90 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 6.58 (m, 2H), 6.52 (d, J = 6.9 Hz, 2H), 6.10 (bs, 1H), 4.26 (bs, 2H), 3.80 (s, 2H), 2.08 (d, J = 1.9 Hz, 2H).  | 3, 33 |
| 387 | 532 |   | CH | CH | H | N{(2-Amino-phenyl)-3-[4-[(3-cyano)-phenylamino)-methyl]-phenyl)-acrylamide                   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.38 (s, 1H), 7.58 (d, J = 7.7 Hz, 2H); 7.54 (d, J = 15.9 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.92-6.83 (m, 5H), 6.75 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 4.95 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).   | 3, 33 |
| 388 | 533 |   | CH | CH | H | 3-[4-[(3-Acetylamino)-methyl]-phenylamino]-methyl)-phenyl)-N(2-amino-phenyl)-acrylamide      | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.37 (bs, 1H), 8.21 (t, J = 5.8 Hz, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.53 (d, J = 15.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.1 Hz, 1H), 6.97 (m, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (dd, J = 1.4, 8.0 Hz, 1H), 6.58 (dt, J = 1.4, 8.0 Hz, 1H), 6.50 (bs, 1H), 6.41 (d, J = 8.0 Hz, 2H), 6.30 (t, J = 6.0 Hz, 1H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H), 4.09 (d, J = 6.0 Hz, 2H), 1.83 (s, 3H). | 3, 33 |

| Ex. | Cpd | W | Y  | Z  | R | Name  | Characterization   | Schm     |
|-----|-----|---|----|----|---|---|--|----------|
| 389 | 534 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-((4-nitro-3-trifluoromethyl-phenylamino)-methyl)-phenyl)-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.37 (bs, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67-6.55 (m, 4H), 5.84 (t, J = 5.8 Hz, 1H), 4.94 (bs, 2H), 4.22 (d, J = 5.8 Hz, 2H). | 3, 33    |
| 390 | 535 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-((3,5-dichloro-phenylamino)-methyl)-phenyl)-acrylamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.39 (bs, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 15.7 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.1 Hz, 1H), 6.97-6.89 (m, 2H), 6.87 (d, J = 15.7 Hz, 1H), 6.75 (dd, J = 1.4, 8.0 Hz, 1H), 6.60-6.55 (m, 4H), 4.95 (bs, 2H), 4.33 (d, J = 6.0 Hz, 2H).                            | 3, 33    |
| 391 | 536 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-((2-(3,4,5-trimethoxy-phenyl)-vinyl)-phenyl)-acrylamide             | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.12 (bs, 1H), 7.64 (d, J = 14.2 Hz, 1H), 7.42 (bs, 4H), 7.23 (bs, 2H), 6.97 (d, J = 14.2 Hz, 1H), 6.94-6.82 (m, 4H), 6.70 (s, 2H), 4.11 (bs, 2H), 3.87 (s, 6H), 3.84 (s, 3H).   | 3        |
| 392 | 537 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-((2-(3,4,5-trimethoxy-phenyl)-vinyl)-phenyl)-acrylamide             | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 8.49 (s, 1H), 7.58 (d, J = 15.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (m, 4H), 7.00 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 5.0 Hz, 2H), 6.69 (d, J = 5.0 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 6.53 (bs, 2H), 6.47 (s, 2H), 3.85 (s, 3H), 3.63 (s, 6H).   | 3        |
| 393 | 538 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-((3-sulfamoyl-phenylamino)-methyl)-phenyl)-acrylamide               | <sup>1</sup> H-NMR (CD <sub>3</sub> OD/CDCl <sub>3</sub> ), δ (ppm): 7.61 (d, J = 15.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 (dd, J = 8.0 Hz, 2H), 7.12 (d, J = 15.7 Hz, 1H), 7.10 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.83-6.66 (m, 4H), 3.93 (bs, all NH signals).  | 1, 3, 33 |

| Ex. Cpd | W | Y  | Z  | R | Name  | Characterization  | Schm      |
|---------|---|----|----|---|---|---|-----------|
| 394 539 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(3-(3-morpholin-4-yl-propyl)sulfamoyl)-phenylamino]-methyl)-phenyl)-acrylamide | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.34 (bs, 1H), 7.64 (d, J = 15.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.34 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 15.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.04 (m, 2H), 6.74 (m, 4H), 4.85 (bs, 1H), 4.30 (d, J = 4.4 Hz, 2H), 3.69 (t, J = 4.4 Hz, 4H), 2.99 (t, J = 5.8 Hz, 2H), 2.40 (bs, 6H), 1.59 (t, J = 4.4 Hz, 2H).          | 3, 33, 42 |
| 395 540 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(2-(3,4,5-trimethoxy-phenyl)-ethyl)-phenyl]-acrylamide                         | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.53 (s, 1H), 7.72 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.33 (m, 1H), 7.16 (d, J = 7.7 Hz, 2H), 7.07 (m, 1H), 6.79 (m, 2H), 6.69 (d, J = 15.6 Hz, 1H), 6.41 (s, 2H), 4.04 (bs, 2H), 3.91 (s, 3H), 3.85 (s, 6H), 2.94 (m, 4H).  | 3, 32     |
| 396 541 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(4-methoxy-phenylamino)-methyl]-phenyl)-acrylamide                             | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.35 (s, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 15.4 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.6 Hz, 2H), 6.58 (m, 1H), 6.52 (d, J = 8.6 Hz, 2H), 5.84 (t, J = 5.5 Hz, 1H), 4.23 (d, J = 5.5 Hz, 2H), 3.61 (s, 3H). | 3, 33     |
| 397 542 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(3,4-dimethoxy-phenylamino)-methyl]-phenyl)-acrylamide                         | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 8.48 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.27 (m, 5H), 6.97 (t, J = 7.5 Hz, 1H), 6.70 (m, 3H), 6.59 (d, J = 15.4 Hz, 1H), 6.25 (s, 1H), 6.12 (d, J = 7.1 Hz, 1H), 4.23 (s, 2H), 3.93 (bs, 3H), 3.75 (s, 3H), 3.73 (s, 3H).  | 3, 33     |
| 398 543 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(3-(1H-tetrazol-5-yl)-phenylamino)-methyl]-phenyl)-acrylamide                  | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.33 (m, 3H), 7.27 (m, 3H), 7.20 (m, 1H), 6.84 (m, 2H), 5.48 (bs, 5H), 4.46 (s, 2H).   | 3, 33     |
| 399 544 |   | CH | CH | H | N-(2-Amino-phenyl)-3-(4-[(4-(1H-tetrazol-5-yl)-methyl)-phenylamino]-methyl)-phenyl)-acrylamide          | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 7.20 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 15.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 5.48 (bs, 5H), 4.39 (s, 2H), 4.16 (s, 2H).  | 3, 33     |



| Ex. Cpd | W | Y  | Z  | R | Name  | Characterization   | Schm  |
|---------|---|----|----|---|---|--|-------|
| 400 545 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-bromo-phenylamino)-methyl]-phenyl}-acrylamide             | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 15.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 15.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.66-6.57 (m, 4H), 4.99 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).  | 3, 33 |
| 401 546 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-bromo-phenylamino)-methyl]-phenyl}-acrylamide             | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.00-6.91 (m, 2H), 6.86 (d, J = 15.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.66-6.54 (m, 4H), 4.93 (bs, 2H), 4.30 (d, J = 5.3 Hz, 2H).   | 3, 33 |
| 402 547 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-iodo-phenylamino)-methyl]-phenyl}-acrylamide              | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.36 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.35 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.57 (t, J = 8.0 Hz, 1H), 6.52 (t, J = 6.0 Hz, 1H), 6.42 (d, J = 8.5 Hz, 2H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H).             | 3, 33 |
| 403 548 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-iodo-phenylamino)-methyl]-phenyl}-acrylamide              | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.40 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 6.92 (m, 3H), 6.84 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.60-6.50 (m, 3H), 4.93 (bs, 2H), 4.28 (d, J = 5.9 Hz, 2H).   | 3, 33 |
| 404 549 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-(2-hydroxyethoxy)-phenylamino)-methyl]-phenyl}-acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.03-6.98 (m, 2H), 6.91 (d, J = 15.3 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 5.9 Hz, 1H), 6.28-6.22 (m, 3H), 4.99 (bs, 3H), 4.61 (s, 2H), 4.34 (d, J = 5.0 Hz, 2H), 4.28 (d, J = 5.0 Hz, 2H). | 3, 33 |

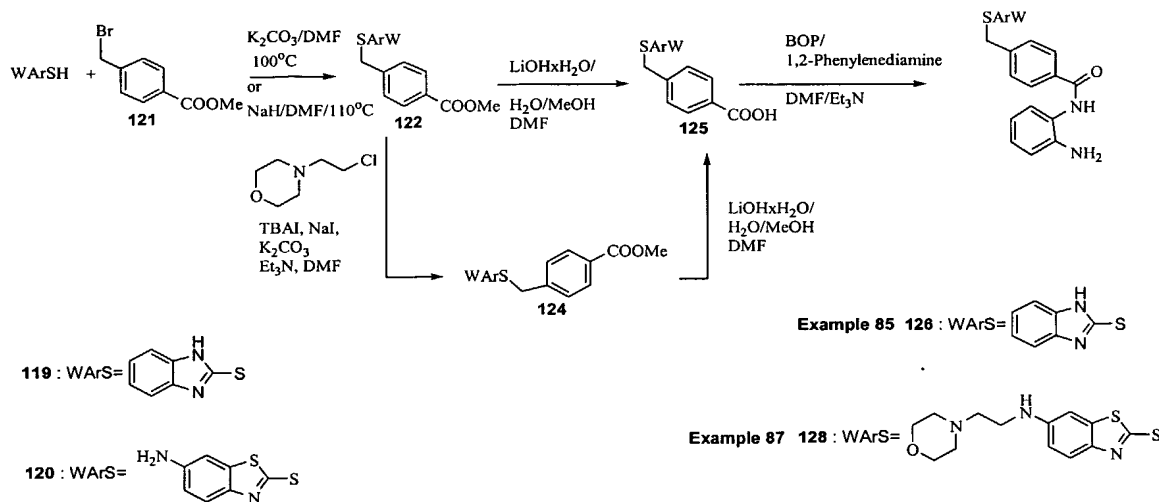
| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization  | Schm  |
|---------|---|----|----|---|--|---|-------|
| 405 550 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>(4-[(4-nitro-<br>phenylamino)-methyl]-<br>phenyl)-acrylamide  | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.38(s, 1H), 7.99 (d, J = 9.1 Hz, 2H), 7.85 (t, J = 5.9 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 6.94-6.92 (m, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 6.58 (t, J = 7.6 Hz, 1H), 4.94 (bs, 2H), 4.46 (d, J = 5.9 Hz, 2H) | 3, 33 |
| 406 551 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>(4-[(3-nitro-<br>phenylamino)-methyl]-<br>phenyl)-acrylamide  | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.37 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.36-7.28 (m, 4H), 7.05-6.98 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 15.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.58 (t, J = 7.6 Hz, 1H), 4.96 (bs, 2H), 4.39 (d, J = 5.3 Hz, 2H)   | 3, 33 |
| 407 552 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>(4-[(4-chloro-<br>phenylamino)-methyl]-<br>phenyl)-acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.43 (s, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 15.8 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.55 (bs, 2H), 4.99 (bs, 2H), 4.46 (d, J = 5.9 Hz, 2H), 4.35 (d, J = 5.9 Hz, 2H)    | 3, 33 |
| 408 553 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>(4-[(3-chloro-<br>phenylamino)-methyl]-<br>phenyl)-acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.50 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.43 (m, 1H), 6.93 (d, J = 7.0 Hz, 1H), 6.79 (d, J = 15.4 Hz, 1H), 6.68 (m, 3H), 6.59 (m, 3H), 5.24 (bs, 2H), 4.31 (s, 2H)   | 3, 33 |
| 409 554 |   | CH | CH | H | N-(2-Amino-phenyl)-3-<br>(4-[(4-fluoro-<br>phenylamino)-methyl]-<br>phenyl)-acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.37(s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.41 (m, 1H), 7.01-6.90 (m, 4H), 6.75 (d, J = 7.6 Hz, 1H), 6.67-6.59 (m, 3H), 6.27 (bs, 1H), 4.95 (bs, 2H), 4.27 (s, 2H)  | 3, 33 |

| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization   | Schm  |
|---------|---|----|----|---|--|--|-------|
| 410 555 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(3-methylsulfonyl)-<br>phenylamino]-methyl}-<br>phenyl}-acrylamide | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD) δ (ppm): 7.64 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (d, J = 7.8 Hz, 1H), 4.29 (s, 2H), 4.05 (bs, 4H), 2.37 (s, 3H).                 | 3, 33 |
| 411 556 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(4-methylsulfonyl)-<br>phenylamino]-methyl}-<br>phenyl}-acrylamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.60-6.54 (m, 3H), 6.39 (t, J = 5.7 Hz, 1H), 4.93 (bs, 2H), 4.29 (d, J = 6.1 Hz, 2H), 2.32 (s, 3H).          | 3, 33 |
| 412 557 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(5-bromo-pyridin-2-<br>ylamino)-methyl]-<br>phenyl}-acrylamide     | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.36 (s, 1H), 8.02 (d, J = 1.7 Hz, 1H), 7.57-7.50 (m, 4H), 7.38-7.32 (m, 4H), 6.92 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 16.3 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 4.94 (bs, 2H), 4.48 (d, J = 5.7 Hz, 2H).  | 3, 33 |
| 413 558 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(naphthalen-1-<br>ylaminomethyl)-<br>phenyl]-acrylamide            | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.37 (s, 1H), 8.25 (m, 1H), 7.76 (m, 1H), 7.57 (m, 2H), 7.47 (m, 4H), 7.33 (d, J = 7.0 Hz, 1H), 7.17 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 5.3 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 4.90 (s, 2H), 4.54 (d, J = 5.3 Hz, 2H). | 3, 33 |
| 414 559 |   | CH | CH | H | N(2-Amino-phenyl)-3-<br>{4-[(3-fluoro-<br>phenylamino)-methyl]-<br>phenyl}-acrylamide          | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.39 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.02 (q, J = 7.6 Hz, 1H), 6.90 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (m, 1H), 6.40 (d, J = 8.2 Hz, 1H), 6.29 (m, 2H), 4.90 (s, 1H), 4.29 (bs, 2H), 4.02 (s, 2H).  | 3, 33 |

| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization  | Schm  |
|---------|---|----|----|---|--|---|-------|
| 415 560 |   |    |    |   | N-(2-Amino-phenyl)-3-{3,5-dimethoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide         | <sup>1</sup> H-NMR (CDCl <sub>3</sub> ), δ (ppm): 7.73 (bs, 1H), 7.63 (d, J = 14.9 Hz, 1H), 6.81 (m, 3H), 6.70 (m, 2H), 6.68-6.56 (m, 2H), 6.07 (s, 2H), 4.35 (s, 2H), 3.86 (s, 6H), 3.81 (s, 6H), 3.75 (s, 3H).  | 60    |
| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization  | Schm  |
| 416 561 |   |    |    |   | N-(2-Amino-3-hydroxy-phenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide             | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 9.22 (s, 1H), 9.11 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 15.8 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 15.8 Hz, 1H), 6.78 (t, J = 7.9 Hz, 1H), 6.23 (t, J = 7.9 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 6.09 (t, J = 6.2 Hz, 1H), 5.89 (s, 2H), 4.77 (bs, 2H), 4.27 (d, J = 5.7 Hz, 2H), 5.89 (s, 6H), 5.76 (s, 3H).        | 3, 33 |
| Ex. Cpd | W | Y  | Z  | R | Name   | Characterization  | Schm  |
| 417 562 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(2,3,4-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide                       | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.25 (s, 1H), 7.74 (d, J = 15.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.34-7.29 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.79 (m, 1H), 6.66 (d, J = 15.5 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 4.36 (s, 2H), 4.18 (bs, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H). | 3, 33 |
| 418 563 |   | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-methoxy-3-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl)-phenyl]-acrylamide | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.58 (s, 1H), 7.66 (d, J = 15.4 Hz, 1H), 7.33-7.28 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 7.04 (t, J = 7.0 Hz, 1H), 6.77-6.70 (m, 4H), 6.64 (d, J = 15.4 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 5.90 (s, 2H), 4.27 (s, 2H), 4.25 (s, 2H), 4.08 (bs, 4H), 3.82 (s, 6H), 3.77 (s, 6H).  | 3, 33 |

| Ex. | Cpd | W | Y | Z | R | Name   | Characterization   | Schm  |
|-----|-----|---|---|---|---|--|--|-------|
| 419 | 564 |   |   |   |   | N-(2,3-Diamino-phenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide               | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 7.64 (d, J = 15.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.31-7.24 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 15.4 Hz, 1H), 5.84 (s, 2H), 4.27 (s, 2H), 4.00 (bs, 6H), 3.71 (s, 6H), 3.68 (s, 3H).  | 3, 33 |
| Ex. | Cpd | W | Y | Z | R | Name   | Characterization   | Schm  |
| 420 | 565 |   |   |   |   | N-(2-Amino-phenyl)-3-{4-[(3-fluoro-4-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide          | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.38 (bs, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 8.3 Hz, 1H), 6.94-6.89 (m, 2H), 6.81 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.43-6.38 (m, 2H), 4.94 (bs, 2H), 4.30 (d, J = 5.7 Hz, 2H), 2.28 (s, 3H). | 3, 33 |
| 421 | 566 |   |   |   |   | N-(2-Amino-phenyl)-3-{4-[(4-methylsulfanyl-3-trifluoromethyl-phenylamino)-methyl]-phenyl}-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.39 (bs, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 6.2 Hz, 1H), 6.96-6.90 (m, 4H), 6.82 (d, J = 15.8 Hz, 1H), 6.79-6.74 (m, 1H), 6.58 (t, J = 7.5 Hz, 1H), 4.95 (bs, 2H), 4.35 (d, J = 6.2 Hz, 2H), 2.35 (s, 3H).                           | 3, 33 |
| Ex. | Cpd | W | Y | Z | R | Name   | Characterization   | Schm  |
| 422 | 567 |   |   |   |   | N-(2-Amino-phenyl)-3-{3-nitro-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide           | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.50 (s, 1H), 8.09 (s, 1H), 7.80 (d, J = 15.4 Hz, 1H), 7.81 (s, 2H), 7.34 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 15.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.26 (t, J = 6.2 Hz, 1H), 5.90 (s, 2H), 4.96 (bs, 2H), 4.39 (d, J = 5.7 Hz, 2H), 3.66 (s, 6H), 3.51 (s, 3H).          | 3, 33 |

| Ex. | Cpd | W | Y | Z | R | Name   | Characterization  | Schm      |
|-----|-----|---|---|---|---|--|---|-----------|
| 423 | 568 |   |   |   |   | N{(2-Amino-phenyl)-3-{3-amino-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.29 (s, 1H), 7.72 (d, J = 15.4 Hz, 1H), 7.33 (m, 2H), 6.90 (1H); 6.71 (2H), 6.62 (3H), 5.97 (1H), 5.87 (2H), 5.49 (2H), 4.96 (2H), 4.10 (2H), 3.65 (6H), 3.51 (3H).  | 3, 33     |
| 424 | 569 |   |   |   |   | N{(2-Amino-phenyl)-3-[6-(3,4-dimethoxy-phenyl)-pyridin-3-yl]-acrylamide                    | LRMS: calc: 375.4, found: 376.4   | 3, 15, 33 |
| 425 | 570 |   |   |   |   | N{(4-Amino-thiophen-3-yl)-3-[4-(4-morpholin-4-yl-phenylamino)-methyl]-phenyl}-acrylamide   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.64 (bs, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.60 (d, J=14.0 Hz, 1H), 7.50 (d, J=7.9 Hz, 2H), 6.90 (d, J=15.8 Hz, 1H), 6.15 (d, J=4.0 Hz, 1H), 5.95 (s, 2H), 5.82 (s, 1H), 4.89 (bs, 2H), 4.33 (d, J=5.7 Hz, 2H), 3.71 (s, 6H), 3.57 (s, 3H). | 3, 33, 60 |



### Example 85

#### *N*-(2-Amino-phenyl)-4-(1*H*-benzimidazol-2-ylsulfanylmethyl)-benzamide (compound 126)

##### Step 1: 4-(1*H*-Benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (compound 122)

[0211] Following the procedure described in Example 47, step 2, but using **119** and substituting **121** for **63**, the title compound **122** was obtained in 95% yield. LRMS = 299.1 (M+1).

##### Step 2: *N*-(2-Amino-phenyl)-4-(1*H*-benzimidazol-2-ylsulfanylmethyl)-benzamide (**126**)

[0212] Following the procedure described in Example 1, steps 4 and 5, but substituting **122** for **6**, the title compound **126** was obtained in 62% yield. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.57 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.53 (bs, 2H), 7.36 (bs, 2H), 7.14-7.08 (m, 3H), 6.94 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 6.56 (t, J = 8.0 Hz, 1H), 4.87 (bs, 2H), 4.62 (s, 2H).

### Example 87

#### *N*-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound 128)

##### Step 1: 4-[6-(2-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (**122**)

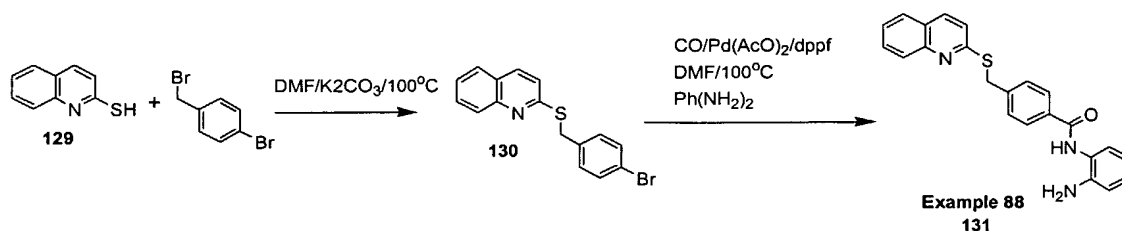
[0213] Following the procedure described in Example 47, step 2, but using **120** and substituting **121** for **63**, the title compound **122** was obtained in 45% yield. LRMS = 331.0 (M+1).

Step 2: 4-[6-(2-Morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (compound **124**)

**[0214]** To a solution of 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester **122** (800 mg, 2.42 mmol), in DMF (24 mL), were added successively solid 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol),  $K_2CO_3$  (611 mg, 5.08 mmol), NaI (363 mg, 2.42 mmol),  $Et_3N$  (370  $\mu$ L, 2.66 mmol) and tetrabutylammonium iodide (894 mg, 2.42 mmol). The mixture was stirred at 120°C for 24h and more 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol) was added. The mixture was stirred for 8h at 120°C and the solvent was removed *in vacuo*. The resulting black syrup was partitioned between  $H_2O$  and EtOAc. The organic layer was successively washed with HCl 1N and saturated aqueous  $NaHCO_3$ . The precipitate was extracted twice with EtOAc, dried over  $MgSO_4$  and concentrated. Purification by flash chromatography (MeOH/ $CHCl_3$ : 5:95 to 10:90) afforded 48 mg (4% yield) of **124** as a light yellow oil. LRMS = 444.1 ( $M+1$ ).

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound **128**)

**[0215]** Following the procedure described in Example 1, steps 4 and 5, but substituting **124** for **6**, the title compound **128** was obtained in 76% yield.  $^1H$  NMR: (Acetone- $d_6$ )  $\delta$  (ppm): 9.06 (bs, 1H), 7.98 (d,  $J = 8.2$  Hz, 2H), 7.63 (d,  $J = 8.5$  Hz, 2H), 7.62 (d,  $J = 8.8$  Hz, 2H), 7.29 (d,  $J = 8.0$  Hz, 1H), 7.06 (d,  $J = 2.2$  Hz, 1H), 7.02-6.97 (m, 1H), 6.87-6.82 (m, 2H), 6.66 (dt,  $J = 7.4$  Hz, 1.4 Hz, 1H), 4.63 (s, 2H), 3.64-3.60 (m, 4H), 3.25 (t,  $J = 6.3$  Hz, 2H), 2.63 (t,  $J = 6.3$  Hz, 2H), 2.54-2.42 (m, 4H).



**N-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (compound **131**)**

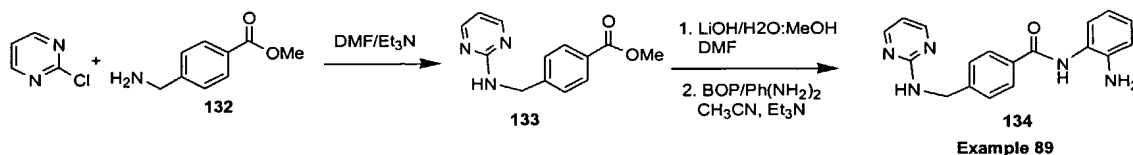
Step 1: 2-(4-Bromo-benzylsulfanyl)-quinoline (compound **130**)

**[0216]** Following the procedure described in Example 47, step 2, but substituting **129** for **63**, the title compound **130** was obtained in 89% yield. LRMS = 332.0 ( $M+1$ ).



Step 2: *N*-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (**131**)

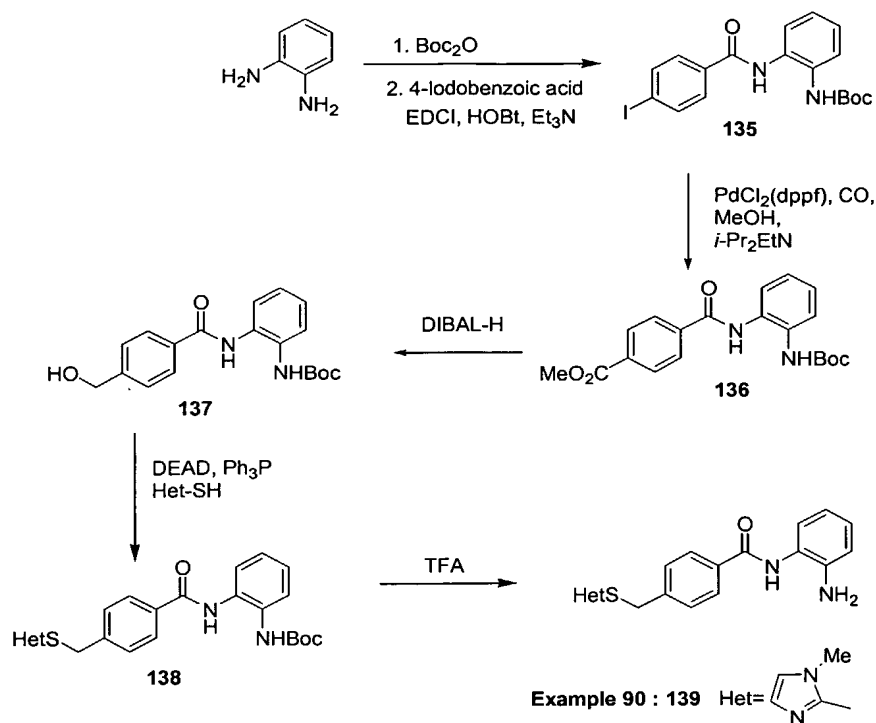
[0217] Following the procedure described in Example 40, step 2, but substituting **129** for **42**, the title compound **131** was obtained in 70% yield. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).

**Example 89*****N*-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (compound **134**)**Step 1: 4-(Pyrimidin-2-ylaminomethyl)-benzoic acid methyl ester (compound **133**)

[0218] Following the procedure described in Example 47, step 2, but substituting **132** for **63**, the title compound **133** was obtained in 76% yield. LRMS = 244.2 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (**134**)

[0219] Following the procedure described in Example 1, steps 4 and 5, but substituting **129** for **6**, the title compound **134** was obtained in 91% yield. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.6 (bs, 1H), 8.32 (d, J = 4.9 Hz, 2H), 7.97 (dt, J = 9.9 Hz, 7.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47, (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).



**Step 1: [2-(4-Iodo-benzoylamino)-phenyl]-carbamic acid *tert*-butyl ester (compound 135)**

**[0220]** To a solution of di-*tert*-butyldicarbonate (39 g, 181 mmol) in THF (139 mL) placed in a water bath, was added 1,2-phenylenediamine (15 g, 139 mmol) and DMAP (1.7 g, 14 mmol). The mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was partitioned between EtOAc and water. The organic layer was washed with HCl 1 N and then with aqueous saturated NaHCO<sub>3</sub>. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated affording the compound (18.9 g, 65% yield) as a light beige powder. LRMS = 209.1 (M+1).

**[0221]** To a solution of 4-iodobenzoic acid (8.0 g, 32.3 mmol) in DMF (65 mL) at r.t., were successively added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.0 g, 41.9 mmol) and 1-hydroxybenzotriazole (5.2 g, 38.7 mmol). The mixture was stirred for 1 h and a solution of (2-amino-phenyl)-carbamic acid *tert*-butyl ester (6.3 g, 30.2 mmol) in DMF (20 mL) was added to the mixture *via* cannula, followed by triethylamine (5.9 mL, 4.9 mmol). The mixture was stirred for 16 h

and the solvent was removed *in vacuo*. The crude material was partitioned between chloroform and water. The organic layer was washed with aqueous saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated to a light brown syrup which was crystallized in hot EtOAc or Et<sub>2</sub>O, yielding **135** (9.3 g, 70% yield) as a white solid. LRMS = 461.0 (M+Na<sup>+</sup>).

Step 2: *N*-(2-*tert*-butoxycarbonylamino-phenyl)-terephthalamic acid methyl ester (compound **136**)

**[0222]** Following the procedure described in Example 40, step 2, but substituting **135** for **42**, the title compound **136** was obtained in 95% yield. LRMS = 393.1 (M+Na<sup>+</sup>).

Step 3: [2-(4-Hydroxymethyl-benzoylamino)-phenyl]-carbamic acid *tert*-butyl ester (**137**)

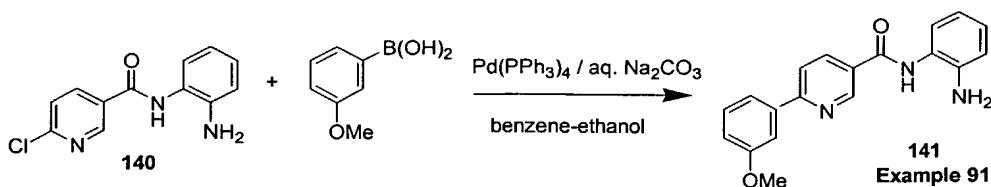
**[0223]** To a solution of **136** (7.5g, 20.6 mmol) in THF (40 mL), cooled down to -20°C under N<sub>2</sub>, was added a 1M solution of DIBAL-H (122 mL, 122 mmol) in toluene. After stirring for 18 h. at r.t., the mixture was cooled down to 0°C and carefully quenched by a dropwise addition of H<sub>2</sub>O (10 mL) and of 2N NaOH (5 mL). The aluminum salts were allowed to decant and the supernatant was removed. The organic layer was washed with H<sub>2</sub>O, 1 N HCl (6 times), satd. aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub> and concentrated (2.04 g, 43%). Purification of the crude material by flash chromatography (EtOAc/hexanes 50:50 to 70:30) afforded **137** (1.14 g, 16% yield) as a solid foam. LRMS = 365.2 (M+Na<sup>+</sup>).

Step 4: {2-[4-(1-Methyl-imidazol-2-ylsulfanylmethyl)-benzoylamino]-phenyl}-carbamic acid *tert*-butyl ester (compound **138**)

**[0224]** To a solution of *N*-methyl-2-mercaptoimidazole (28 mg, 0.25 mmol) in THF (1 mL), at r.t. under N<sub>2</sub> atmosphere were successively added **137** (70 mg, 0.20 mmol), triphenylphosphine (70 mg, 0.27 mmol) followed by dropwise addition of diethyl azodicarboxylate (48 µL, 0.31 mmol). The mixture was stirred for 2 h and the solvent was removed *in vacuo*. Purification by flash chromatography using MeOH/CHCl<sub>3</sub> (5:95) as the eluent afforded the title compound **138** (81 mg), in 91% yield, which was found to contain some diethyl hydrazodicarboxylate residus. The compound was used as is without further purification.

Step 5: *N*-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)-benzamide (compound **139**)

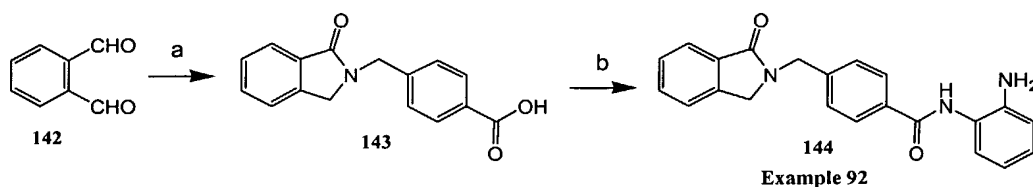
**[0225]** Following the procedure described in Example 42, step 3, but substituting **138** for **46**, the title compound **139** was obtained in 62% yield. <sup>1</sup>H NMR: (Acetone-d<sub>6</sub>) δ (ppm): 9.07 (bs, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.1 Hz, 1H), 7.03-6.96 (m, 2H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.4 Hz, 1.1 Hz, 1H), 4.63 (bs, 2H), 4.29 (s, 2H), 3.42 (s, 3H).



### Example 91

#### **N-(2-Amino-phenyl)-6-(3-methoxyphenyl)-nicotinamide (compound 141)**

**[0226]** To a mixture of 3-methoxyphenyl boronic acid (152 mg, 1.0 mmol) and **140** (248 g, 1.0 mmol) were added benzene (8 mL) and ethanol (4 mL) followed by 2 M  $\text{Na}_2\text{CO}_3$  aqueous solution (3.2 mL, 6.4 mmol). The reaction mixture was stirred under nitrogen for 30 min and then  $\text{Pd(PPh}_3)_4$  (58 mg, 0.05 mmol) was quickly added. After 24 h of reflux, the mixture was cooled to room temperature, filtered through a pad of celite and rinsed with ethyl acetate (30 mL). The organic solution was washed with brine (5 mL), dried ( $\text{MgSO}_4$ ), and concentrated. Purification by flash silica gel chromatography (Hexane/Ethyl acetate: 1/1) afforded **141** (302 mg, 95% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 9.11 (d,  $J = 1.8$  Hz, 1H), 8.30 (dd,  $J = 8.4$  Hz, 1.8 Hz, 1H), 7.57 (d,  $J = 8.4$  Hz, 1H), 7.52-7.47 (m, 1H), 7.36 (m, 1H), 7.22 (m, 1H), 7.09-6.78 (m, 4H), 3.84 (s, 3H), 3.39 (br s, 2H).



a. p-aminomethylbenzoic acid/AcOH/5 min/reflux  
b. HOBt/EDC/1,2-diamino benzene

### Example 92

#### **N-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144)**

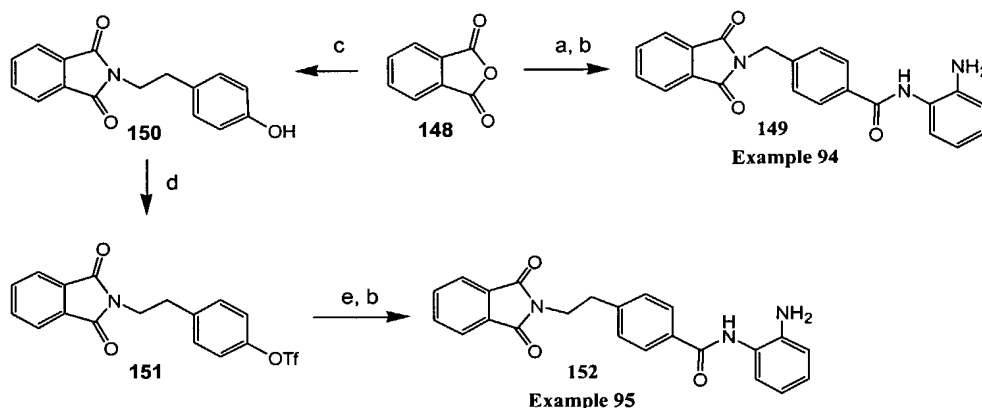
##### Step 1: 4-(1-Oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzoic acid (compound 143)

**[0227]** To a solution of benzene-1,2-carbaldehyde **142** (1.0 g, 7.46 mmol) in 10 mL of acetic acid was added 4-aminomethylbenzoic acid (1.13 g, 7.46 mmol). The reaction mixture was refluxed 5 min and cooled to the room temperature. A crystalline precipitate was formed and triturated with  $\text{CH}_2\text{Cl}_2$  to produce the title compound **143** (1.29 g, 49%).

##### Step 2: N-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144)

**[0228]** To a solution of the carboxylic acid (0.32 g, 0.89 mmol) in DMF (8 mL) at rt, was added HOBt (0.16 g, 1.15 mmol) and EDC (0.25 g, 1.33 mmol) and the solution was stirred for 1.5 h.

Lastly, phenylenediamine (0.12 g, 1.07 mmol) was added and the mixture was allowed to stir for 18-20 h. DMF was removed *in vacuo* and the crude was partitioned between ethyl acetate and H<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH (19:1)) afforded **144** in 46% yield. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>)  $\delta$  9.71 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.55-7.70 (m, 3H), 7.46 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 4.93 (bs, 2 H), 4.87 (s, 2 H), 4.47 (s, 2H).



- a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
- b. HOBT/EDC/1,2-diamino benzene
- c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
- d. PhNTf<sub>2</sub>/NaH/THF-DMF/30 min/0°C
- e. 1. CO/Pd(OAc)<sub>2</sub>/dppf/Et<sub>3</sub>N/MeOH-DMF/4 days/75°C  
2. AcOH/HCl/3 hrs/reflux

### Example 94

#### **N-(2-Amino-phenyl)- 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 149)**

**[0229]** Phthalic anhydride **148** (1.3 g, 8.9 mmol) and 4-aminomethylbenzoic acid in 20 mL acetic acid were refluxing for 3 h, cooled to the room temperature and evaporated to yield a solid residue which was triturated with water, filtered off and dried to produce the intermediate carboxylic acid (1.7 g, 68%). LMRS = 282.0 (M+1).

**[0230]** Following a procedure analogous to that described in Example 92, step 2, but substituting the acid for **143**, the title compound **149** was obtained in 17% yield. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>)  $\delta$  9.59 (s, 1H), 7.82-7.91 (m, 6H), 7.40 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 7.4 Hz, 1H), 4.83 (bs, 4H).

## Example 95

**N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)**Step 1: 2-[2-(4-Hydroxy-phenyl)-ethyl]-isoindole-1,3-dione (compound 150)

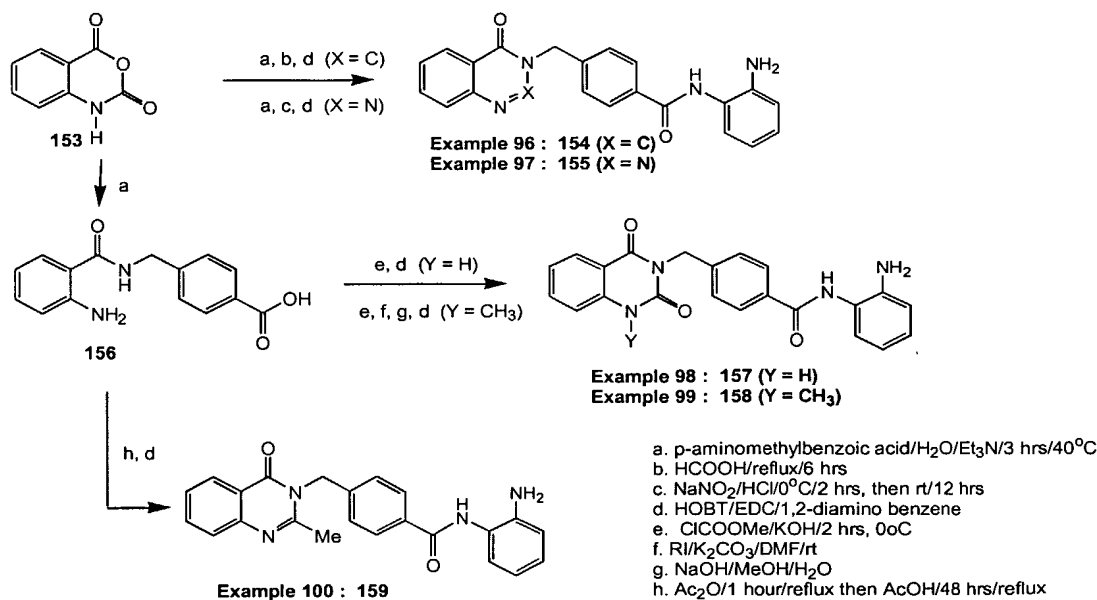
[0231] Following a procedure analogous to that described in Example 94, step 1, but substituting 4-aminomethylbenzoic acid for tyramine the title compound **150** was obtained in 48% yield. LMRS = 268.0 (M+1).

Step 2: 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl]-phenyl trifluoromethane-sulfonate (151)

[0232] To a solution of sodium hydride (90 mg, 25 mmol) in dry THF (20 mL) at 0°C, **150** (500 mg, 8.9 mmol) was added followed by the addition of dry DMF (2 mL). The reaction mixture was stirred for 20 min at 0°C, treated portionwise with PhN(Tf)<sub>2</sub>, stirred for additional 2 h and evaporated to produce a solid material which was purified by chromatography on a silica gel column, (CH<sub>2</sub>Cl<sub>2</sub> – MeOH (19:1)) to provide **151** (639 mg, 86% yield). LMRS = 400.0 (M+1).

Step 3: N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

[0233] Following a procedure analogous to that described in Example 40, step 2, but substituting **151** for **42**, the title compound **152** was obtained in 15% yield. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>)  $\delta$  9.57 (s, 1H), 7.78-7.87 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 6.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.83 (bs, 2 H), 3.85 (t, J = 7.1 Hz, 2 H), 3.00 (t, J = 7.1 Hz, 2 H).



**Example 96*****N*-(2-Amino-phenyl)-4-(4-oxo-4*H*-quinazolin-3-ylmethyl)-benzamide (compound 154)**

**[0234]** A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et<sub>3</sub>N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride **153** (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and evaporated to form an oily residue, which was refluxing in formic acid (20 mL) for 7 h. Formic acid was removed in vacuum to produce a solid, which was triturated with water and filtered off to provide the carboxylic acid (1.61 g, 96%). LMRS = 281.0 (M+1).

**[0235]** Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **154** was obtained in 43% yield. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.71 (s, 1H), 8.68 (s, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.4, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.35 (s, 2 H).

**Example 97*****N*-(2-Amino-phenyl)-4-(4-oxo-4*H*-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide (compound 155)**

**[0236]** A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et<sub>3</sub>N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and cooled to 0°C. The cold reaction mixture was acidified with conc. HCl (5 mL) and treated drop wise with NaNO<sub>2</sub> solution (520 mg, 7.5 mmol in 5 mL water) over 5 min period of time, then left overnight at room temperature. A precipitate formed which was collected, washed with water and dried to provide the carboxylic acid (1.62 g, 96%). LMRS = 282.0 (M+1).

**[0237]** Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **155** was obtained in 27% yield. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.62 (s, 1H), 8.25 (t, J = 6.7 Hz, 2H), 8.11 (ddd, J = 7.1 Hz, 1.4 Hz, 1H), 7.93-7.98 (m, 3H), 7.49 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.66 (s, 2 H), 4.87 (bs, 2 H).

**Example 98*****N*-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzamide  
(compound **157**)**

Step 1: 4-[(2-Amino-benzoylamino)-methyl]-benzoic acid (compound **156**)

**[0238]** To a suspension of 4-aminomethylbenzoic acid (5.09 g, 33.7 mmol) in H<sub>2</sub>O (50 mL), was added Et<sub>3</sub>N (4.7 mL, 33.7 mmol) followed by isatoic anhydride **153** (5.0 g, 30.6 mmol). The brown mixture was heated at 40°C for 2 h until the mixture became homogeneous and then Et<sub>3</sub>N was removed *in vacuo*. The resulting aqueous solution was acidified (10% HCl/H<sub>2</sub>O) and the mixture was partitioned between H<sub>2</sub>O and ethyl acetate. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give **156** as a white solid (6.0 g, 72 %). LMRS = 271.0 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzamide (compound **157**)

**[0239]** The carboxylic acid **156** (1.72 g, 6.36 mmol) was suspended in a solution of NaOH (2.55 g, 63.6 mmol) in H<sub>2</sub>O (12 mL). To this solution was added dioxane (10 mL) until mixture became homogeneous. The solution was cooled to 0°C in an ice-bath and methyl chloroformate (1.25 mL, 16.1 mmol) was added portionwise over 2 h. After completion of the reaction, the excess methyl chloroformate and dioxane were removed *in vacuo* and the mixture was diluted with methanol (80 mL) and H<sub>2</sub>O (20 mL). The solution was heated to 50°C for 1 h. until the cyclization was complete. Methanol was removed *in vacuo* and then the aqueous layer was extracted with ethyl acetate. Subsequently, the aqueous phase was acidified (10% HCl/H<sub>2</sub>O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. The resulting crude was triturated with warm methanol to afford the carboxylic acid as a white solid (1.7 g, 90%). LMRS = 319.0 (M+Na).

**[0240]** Following a procedure analogous to that described in Example 92, step 2, but substituting the quinazolinedione carboxylic acid for **143**, the title compound **157** was obtained. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 11.56 (brs, 1H), 9.59 (brs, 1H), 7.96-7.88 (m, 3H), 7.67 (dt, J = 8.4, 1.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.57 (t, J = 6.9 Hz, 1H), 5.15 (brs, 2H), 4.86 (brs, 2H).



**Example 99****N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)**

Step 2: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid methyl ester

**[0241]** To a solution of the quinazolin-2(1H)-one-4-carboxylic acid (1.0 g, 3.38 mmol) in DMF (7 mL), was added  $K_2CO_3$  (1.4 g, 10.1 mmol) and the mixture was then cooled to 0°C. Subsequently, MeI (1.05 mL, 16.9 mmol) was added and the mixture was allowed to warm to rt in the ice bath overnight. Excess methyl iodide and DMF were removed *in vacuo* and the crude was partitioned between ethyl acetate and  $H_2O$ . The aqueous phase was washed again with ethyl acetate, the combined organic extracts were dried over  $Na_2SO_4$  and then concentrated *in vacuo* to yield the desired product as an off-white solid (0.93 g, 85%). LMRS = 325.0 (M+1).

Step 3: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid

**[0242]** To a suspension of the methyl ester (1.25 g, 3.85 mmol) in methanol (35 mL), was added 1N NaOH (30 mL, 38.5 mmol) and the mixture was heated to 45-50°C for 3 h. until it became homogeneous. Methanol was removed *in vacuo* and the crude was partitioned between ethyl acetate and  $H_2O$ . The aqueous phase was acidified (10% HCl/ $H_2O$ ) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were dried over  $Na_2SO_4$  and concentrated *in vacuo* to afford product 5 as a white solid (1.15 g, 96%). LMRS = 311.0 (M+1).

Step 4: N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)

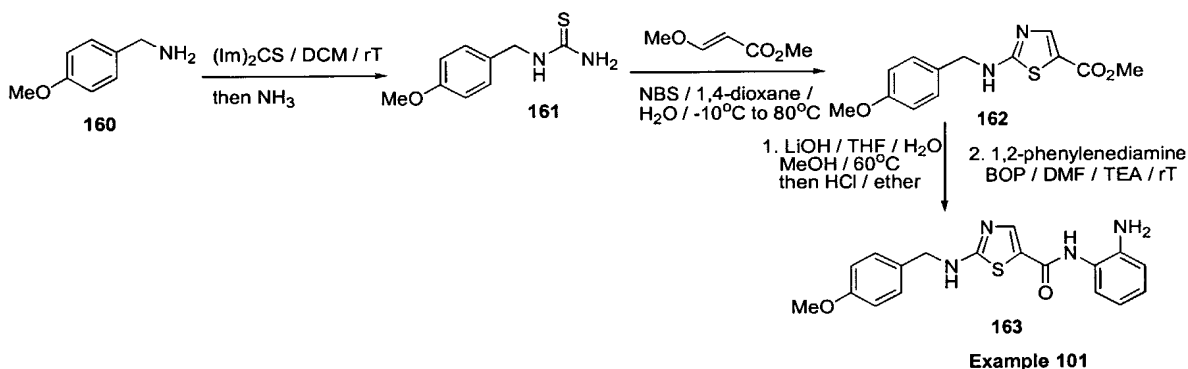
**[0243]** Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **158** was obtained in 10% yield.  $^1H$  NMR: (DMSO- $d_6$ )  $\delta$  9.59 (brs, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.80 (dt, J = 6.9, 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.21 (brs, 2H), 4.86 (brs, 2H), 3.54 (s, 3H).

**Example 100****N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 159)**

**[0244]** A suspension of **156** (903 mg, 3.34 mmol) in acetic anhydride (15 mL) was heated at 50°C for 1 h. Acetic anhydride was evaporated under vacuum and the solid material formed was

dissolved in acetic acid (30 mL). This solution was refluxed 48h and evaporated to form another solid material, which was recrystallized from a mixture AcOEt/CHCl<sub>3</sub> to produce the intermediate carboxylic acid (420 mg, 43% yield). LMRS = 385.0 (M+1).

**[0245]** Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **159** was obtained in 49 % yield. <sup>1</sup>H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H, overlaps with the DMSO signals).



### Example 101

#### ***N*-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound 163)**

##### Step 1: 4-Methoxybenzyl-thiourea (compound 161)

**[0246]** To a solution of thiocarbonyl diimidazole (1.23g, 6.22 mmol, 1.5 equiv.) in dry dichloromethane (10 mL), neat alkylamine **160** (4.15 mmol, 1.0 equiv.) was added dropwise at 0°C, and the solution stirred from 0°C to 15°C during 16 h. A solution of concentrated ammonium hydroxide (3 mL, 45 mmol, 3.6 equiv.) in 1,4-dioxane (6 mL) was added at 0°C and stirred at room temperature for 7 h. The solution was diluted with ethyl acetate (250 mL), washed with brine (2 x 50 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. After purification by column chromatography (silica gel, elution 5% methanol in dichloromethane), **161** was obtained as yellow solid (700.2 mg, 3.6 mmol, 86% yield). <sup>1</sup>H NMR: (Acetone-d<sub>6</sub>) δ (ppm): 7.53 (bs, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.67 (bs, 2H), 4.67 (s, 2H), 3.77 (s, 3H). LMRS = 197.1 (M+1).

Step 2: 2-(4-Methoxybenzylamino)thiazole-5-carboxylic acid methyl ester (compound **162**)

[0247] A solution of trans methyl-2-methoxyacrylate (461 mg, 3.97 mmol, 1 equiv.) in 50% 1,4-dioxane in water (4 mL) stirred at -10°C, was treated with *N*-bromosuccinimide (792 mg, 4.46 mmol, 1.12 equiv.), stirred at the same temperature for 1h, transferred to a flask containing the thiourea **161** (700.2 mg, 3.6 mmol) and the mixture was stirred at 80°C for 2h. After cooling down to room temperature, concentrated NH<sub>4</sub>OH (0.8 mL) was added, stirred for 10 min and the resulting precipitated filtered and washed with water, giving 363 mg (1.3 mmol, 36% yield) of **162**, plus 454 mg additional (91 % pure by HPLC) as residue from evaporation of the filtrated (ca. 77% overall yield). <sup>1</sup>H NMR: (Acetone-d<sub>6</sub>) δ (ppm): 7.97 (bs, 1H), 7.72 (bs, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H). LMRS = 279.1 (M+1).

Step 3: *N*-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound **163**)

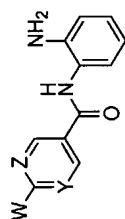
[0248] Following the procedure described in Example 1, steps 4 and 5, but substituting **162** for **6**, the title compound **163** was obtained in 50% yield. <sup>1</sup>H-NMR (methanol-*d*<sub>4</sub>) δ (ppm): 7.86 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.04 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.86 (m, 1H), 6.74 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.85 (bs, 4H), 4.45 (s, 2H), 3.78 (s, 3H).

**Examples 102-121**

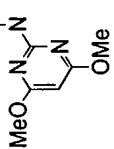
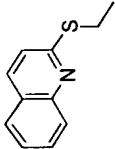
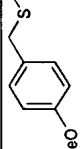
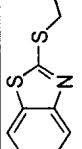
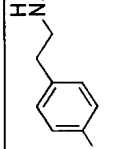
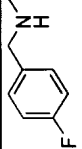
[0249] Examples 102 to 121 describe the preparation of compounds **164** to **183** using the same procedures as described for compounds **62** to **163** in Examples 47 to 101. Characterization data are presented in Tables 4a and 4b.

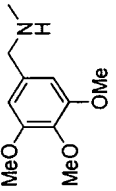
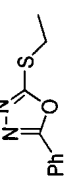
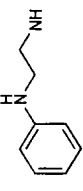
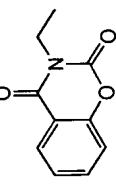
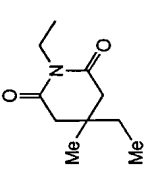
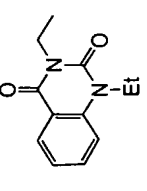
Table 4a

## Characterization of Compounds Prepared in Examples 102-121



| Ex. | Cpd | W | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 102 | 164 |   | CH | CH | N-(2-Amino-phenyl)-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-benzamide | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 9.09 (bs, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.00 (t, J = 6.6 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 5.99 (s, 2H), 5.46 (bs, 1H), 4.64 (bs, 2H), 4.43 (s, 2H), 3.69 (s, 6H), 3.60 (s, 3H). | 11   |
| 103 | 165 |   | N  | CH | N-(2-Amino-phenyl)-6-(3-hydroxymethyl-phenyl)-nicotinamide             | <sup>1</sup> H NMR (20% CD <sub>3</sub> OD in CDCl <sub>3</sub> ) δ (ppm): 9.14 (d, J = 1.8 Hz, 1H), 8.33 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.93 (s, 1H), 7.82 (m, 2H), 7.50-7.40 (m, 2H), 7.22-6.45 (m, 4H), 4.69 (s, 2H).  | 15   |
| 104 | 166 |   | CH | CH | N-(2-Amino-phenyl)-4-(3-methoxy-phenyl)-benzamide                      | <sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.98 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.31-7.04 (m, 5H), 6.92-6.80 (m, 3H), 3.84 (s, 3H).   | 15   |
| 105 | 167 |   | CH | N  | N-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide              | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.33 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 5.8 Hz, 1H), 7.24 (d, J = 8.52 Hz, 2H), 7.11 (d, J = 7.69 Hz, 1H), 6.90 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.50-6.58 (m, 2H), 4.83 (s, 2H), 4.45 (d, J = 5.8 Hz, 2H), 3.70 (s, 3H).   | 6    |
| 106 | 168 |   | CH | N  | N-(2-amino-phenyl)-6-[2-(4-methoxy-phenyl)-ethylamino]-nicotinamide    | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 8.72 (d, J = 2.5 Hz, 1H), 7.97 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 7.23 (m, 4H), 6.81-7.03 (m, 4H), 6.64 (m, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.92 (s, 2H), 3.78 (s, 3H), 3.55 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H).   | 6    |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 107 | 169 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dimethoxy-pyrimidin-2-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.63 (bs, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.85-7.82 (m, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.03 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.9 Hz, 7.7 Hz, 1H), 4.94 (bs, 2H), 4.54 (d, J = 6.0 Hz, 2H), 3.79 (bs, 6H).  | 11   |
| 108 | 170 |    | CH | CH | N-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide                | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).       | 11   |
| 109 | 171 |    | N  | CH | N-(2-Amino-phenyl)-6-(4-methoxy-benzylsulfanylmethyl)-nicotinamide          | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.06 (bs, 1H), 8.17 (dt, J = 10.9 Hz, 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.21-7.13 (m, 2H), 7.01 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 5.01 (bs, 2H), 4.47 (s, 2H), 3.76 (s, 3H).                                      | 12   |
| 110 | 172 |    | CH | CH | N-(2-Amino-phenyl)-4-(benzothiazol-2-ylsulfanylmethyl)-benzamide            | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 8.01 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.90 (dd, J = 4.4 Hz, 0.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.48 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 7.37 (td, J = 7.1 Hz, 1.1 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.58 (t, J = 6.6 Hz, 1H), 4.88 (s, 2H), 4.73 (s, 2H). | 11   |
| 112 | 174 |  | CH | N  | N-(2-amino-phenyl)-6-[2-(4-fluoro-phenyl)-ethylamino]-nicotinamide          | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.34 (s, 1H), 8.64 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 9 Hz, 2 Hz, 1H), 7.16-7.22 (m, 3H), 7.06-7.20 (m, 3H), 6.90-6.96 (m, 1H), 6.72-6.78 (m, 1H), 6.46-6.60 (m, 2H), 4.92 (s, 2H), 3.50 (m, 2H), 2.92 (m, 2H).   | 6    |
| 113 | 175 |  | CH | N  | N-(2-amino-phenyl)-6-(4-fluoro-benzylamino)-nicotinamide                    | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.34 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 7.91 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.66 (t, J = 6 Hz, 1H), 7.32-7.37 (m, 2H), 7.08-7.38 (m, 3H), 6.93 (m, 1H), 6.74 (m, 1H), 6.52-6.58 (m, 2H), 4.84 (s, 2H), 4.51 (d, J = 6.0 Hz)  | 6    |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization  | Schm |
|-----|-----|---|----|----|---|---|------|
| 114 | 176 |    | CH | N  | N-(2-amino-phenyl)-6-(3,4,5-trimethoxybenzylamino)nicotinamide                          | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.34 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 6 Hz, 1H), 7.10 (m, 1H), 6.93 (m, 1H), 6.74 (m, 1H), 6.66 (s, 2H), 6.56 (m, 2H), 4.84 (s, 2H), 4.45 (d, J = 6 Hz, 2H), 3.73 (s, 6H), 3.31 (s, 3H).   | 6    |
| 115 | 177 |    | CH | CH | N-(2-Amino-phenyl)-4-(5-phenyl-1,3,4-oxadiazol-2-ylsulfanylmethyl)-benzamide            | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 9.08 (bs, 1H), 8.02 (dd, J = 7.1 Hz, 1.9 Hz, 4H), 7.69 (d, J = 8.5 Hz, 2H), 7.62-7.57 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, J = 6.6 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 4.70 (s, 2H), 4.63 (bs, 2H).   | 14   |
| 116 | 178 |    | N  | CH | N-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide                             | <sup>1</sup> H-NMR (CD <sub>3</sub> OD-d <sub>4</sub> ) δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, J = 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H). | 11   |
| 117 | 179 |    | CH | CH | N-(2-Amino-phenyl)-4-(2,4-dioxo-4H-benzole[1,3]oxazin-3-ylmethyl)-benzamide             | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.62 (s, 1H), 8.00 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 7.80-7.92 (m, 3H), 7.42-7.50 (m, 4H), 7.13 (d, J = 7.1 Hz, 1H), 6.95 (ddd, J = 8.0 Hz, 1.6 Hz, 1H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.13 (s, 2H), 4.87 (bs, 2H).  | 11   |
| 118 | 180 |  | CH | CH | N-(2-Amino-phenyl)-4-(4-ethyl-4-methyl-2,6-dioxopiperidin-1-ylmethyl)-benzamide         | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.86 (bs, 2H), 2.61 (s, 2H), 2.55 (s, 2H), 1.31 (q, J = 7.7 Hz, 2H), 0.91 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H).                                    | 11   |
| 119 | 181 |  | CH | CH | N-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide | <sup>1</sup> H NMR: (CDCl <sub>3</sub> ) δ (ppm): 8.23 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (dt, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H).  | 19   |

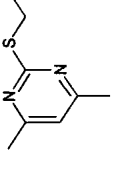
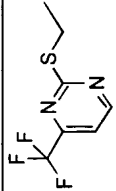
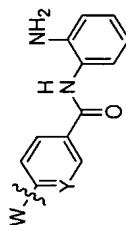
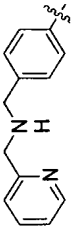
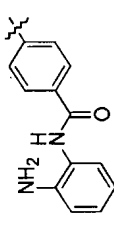
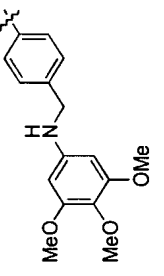
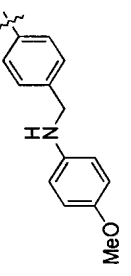
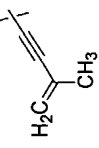
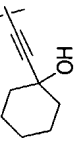
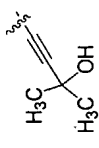
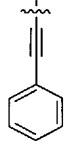
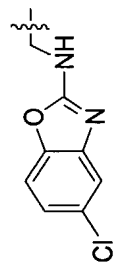
| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization  | Schm |
|-----|-----|---|----|----|---|---|------|
| 120 | 182 |  | CH | CH | N(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide     | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (bs, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).   | 11   |
| 121 | 183 |  | CH | CH | N(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)benzamide | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (bs, 1H), 9.07 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.78 (d, J = 4.7 Hz, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.64 (dt, J = 7.4 Hz, 7.1 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H). | 11   |

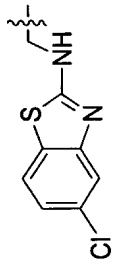
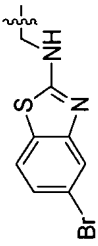
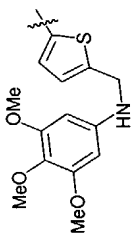
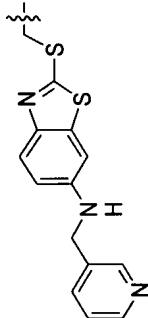
Table 4b

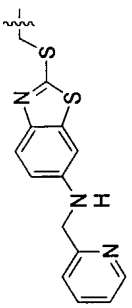
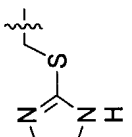

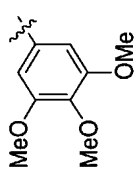
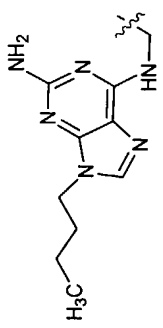


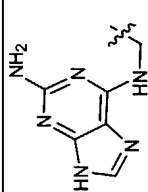
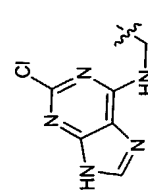
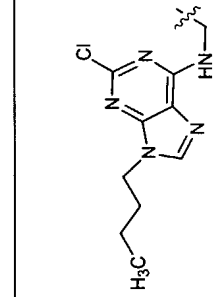
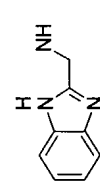
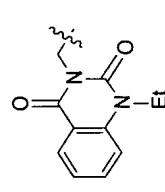
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 123 | 187 |    | CH | CH | N(2-Amino-phenyl)-4-[3-(pyridin-2-ylmethyl)-aminomethyl]phenyl-benzamide         | <sup>1</sup> H NMR (20% CD <sub>3</sub> OD in CDCl <sub>3</sub> ) δ (ppm): 8.46 (m, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.64-6.70 (m, 14 H), 3.80 (br s, 4H).   | 21   |
| 124 | 188 |  | CH | CH | Biphenyl-4,4'-dicarboxylic acid bis-[(2-amino-phenyl)-amide]                     | <sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 9.80 (bs, 2H), 8.16 (d, J = 7.9 Hz, 4H), 7.96 (d, J = 7.9 Hz, 4H), 7.23 (d, J = 7.4 Hz, 2H), 7.03 (dd, J = 6.9, 7.4 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.66 (dd, J = 6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).   | 1    |
| 125 | 189 |  | CH | CH | N(2-Amino-phenyl)-4-[4-{(3,4,5-trimethoxy-phenylamino)-methyl}-phenyl]-benzamide | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.15 (1H, brs), 8.17 (2H, d, J = 8.0), 7.90 (2H, d, J = 8.2), 7.87 (1H, brs), 7.72 (1H, d, J = 6.6), 7.54 (2H, m), 7.40 (1H, d, J = 8.5), 7.25 (1H, m), 7.16 (1H, d, J = 7.4), 7.07 (1H, m), 6.08 (2H, s), 4.42 (2H, s), 3.73 (6H, s), 3.58 (3H, d, J = 0.8) | 21   |

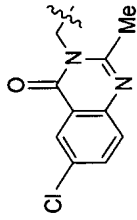
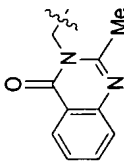
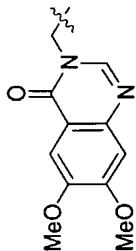
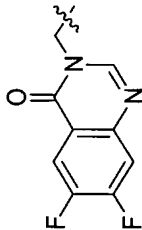
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 126 | 190 |    | CH | CH | N(2-Amino-phenyl)-4-[4-((4-methoxyphenylamino)-methyl)-phenyl]-benzamide | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (1H, brs), 8.17 (2H, d, J=7.7), 7.88 (3H, m), 7.76 (1H, d, J=7.1), 7.52 (2H, m), 7.35 (1H, d, J=8.0), 7.17 (1H, m), 7.08-6.93 (6H, m), 4.50 (3H, s), 3.75 (2H, s)   | 21   |
| 128 | 193 |    | CH | CH | N(2-Amino-phenyl)-4-(3-methylbut-3-en-1-ynyl)-benzamide                  | LRMS calc: 276.03, found: 277.2 (MH) <sup>+</sup>  | 22   |
| 129 | 194 |    | CH | CH | N(2-Amino-phenyl)-4-(1-hydroxy-2-cyclohexylethynyl)-benzamide            | LRMS calc: 334.4, found: 335 (MH) <sup>+</sup>   | 22   |
| 130 | 195 |    | CH | CH | N(2-Amino-phenyl)-4-(3-hydroxy-3-methylbut-1-ynyl)-benzamide             | LRMS calc: 294.35, found: 295.1 (MH) <sup>+</sup>  | 22   |
| 131 | 196 |    | CH | CH | N(2-Amino-phenyl)-4-phenylethynyl-benzamide                              | LRMS calc: 312.37, found: 313.2 (MH) <sup>+</sup>  | 22   |
| 180 | 320 |  | CH | CH | N(2-Amino-phenyl)-4-[(5-chloro-benzooxazol-2-ylamino)-methyl]-benzamide  | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 9.67 (s, 1H), 8.85 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.3 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (t, 7.0 Hz, 1H), 4.94 (s, 2H), 4.67 (d, J = 5.3 Hz, 2H). | 35   |

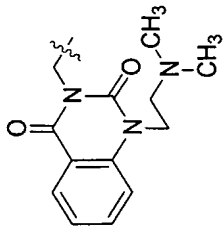
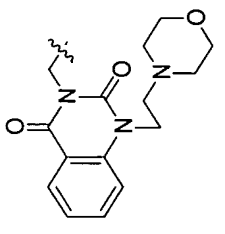
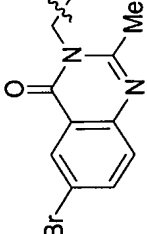


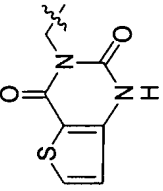
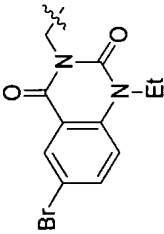
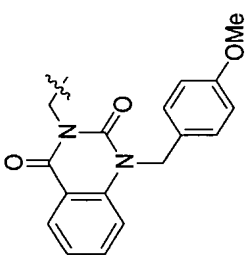
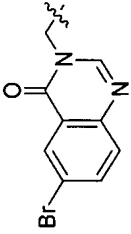
| Ex. | Cpd | W  | Y  | Z  | Name  | Characterization   | Schm      |
|-----|-----|--|----|----|---|--|-----------|
| 181 | 321 |   | CH | CH | N-(2-Amino-phenyl)-4-((4-chlorophenyl)thiazol-2-ylamino)methylbenzamide                     | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.67 (bs, 1H), 8.36 (t, J = 5.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.02 (t, J = 8.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 7.1 Hz, 1H), 4.92 (bs, 2H), 4.65 (d, J = 5.8 Hz, 2H).                  | 35        |
| 182 | 322 |   | CH | CH | N-(2-Amino-phenyl)-4-((5-bromobenzothiazol-2-ylamino)methylbenzamide                        | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 6.97 (s, 1H), 8.78 (bs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 8.00 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.43-7.35 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 4.94 (s, 2H), 7.74 (d, J = 5.9 Hz, 2H).                                      | 33,<br>34 |
| 183 | 323 |   | CH | CH | N-(2-Amino-phenyl)-4-((3,4,5-trimethoxyphenylamino)methylthiophen-2-ylmethylbenzamide       | LRMS calc: 489.58, found: 490 (MH) <sup>+</sup>  | 21        |
| 184 | 325 |  | CH | CH | N-(2-Amino-phenyl)-4-((6-(pyridin-3-ylmethyl)amino)benzothiazol-2-ylsulfanylmethylbenzamide | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 8.65 (d, J = 1.4 Hz, 1H), 8.44 (dd, J = 4.7, 3.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.81-7.77 (m, 1H), 7.63 (m, 3H), 7.33-7.26 (m, 2H), 7.09 (d, J = 2.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.86 (dd, J = 8.0, 1.4 Hz, 1H), 6.69-6.64 (m, 1H), 4.64 (s, 2H), 4.47 (s, 2H). | 11        |

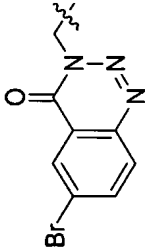
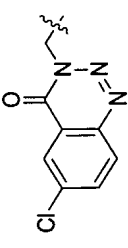
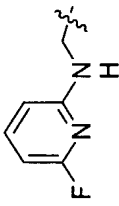
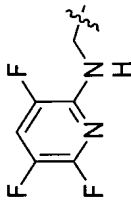
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization  | Schm   |
|-----|-----|---|----|----|--|---|--------|
| 185 | 326 |    | CH | CH | N(2-Amino-phenyl)-4-[6-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-ylsulfanylmethyl]-benzamide | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H), 8.52-8.51 (m, 1H), 7.89 (d, J = 8.24 Hz, 2H), 7.71 (td, J = 7.7, 1.9 Hz, 1H), 7.59-7.53 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.12 (d, J = 6.9 Hz, 1H), 6.98-6.96 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.81 (dd, J = 9.1, 2.5 Hz, 1H), 6.76-6.73 (m, 1H), 6.67 (t, J = 5.8 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.87 (s, 1H), 4.58 (s, 2H), 4.38 (d, J = 6.3 Hz, 2H). | 11, 34 |
| 186 | 327 |    | CH | CH | N(2-Amino-phenyl)-4-[1H-imidazol-2-ylsulfanylmethyl]-benzamide                                 | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 12.23 (bs, 1H), 9.59 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.14-7.12 (m, 2H), 6.94-6.92 (m, 2H), 6.76 (d, J = 6.6 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H).   | 14     |
| 187 | 328 |    | CH | CH | N(2-Amino-phenyl)-4-morpholin-4-ylmethylbenzamide  | <sup>1</sup> H NMR: (CD <sub>3</sub> OD) δ (ppm): 8.03 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 7.16 (t, J = 6.6 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 3.78 (t, J = 4.4 Hz, 4H), 3.68 (s, 2H), 2.57-2.54 (m, 4H).  | 37     |
| 188 | 329 |   | CH | CH | 3',4',5'-Trimethoxybiphenyl-4-carboxylic acid (2-amino-phenyl)-amide                           | <sup>1</sup> H NMR: (CD <sub>3</sub> OD) δ (ppm): 8.14 (d, J = 7.9 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.17 (t, J = 7.0 Hz, 1H), 7.04 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 4.95 (s, 6H), 4.01 (s, 3H).   | 37     |
| 189 | 330 |  | CH | CH | 4-[(2-Amino-9-butyl-9H-purin-6-ylamino)methyl]-N-(2-amino-phenyl)-benzamide                    | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.7 Hz, 2H), 7.95 (bs, 2H), 7.78 (s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.3, 8.0 Hz, 1H), 6.8 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 7.3, 7.7 Hz, 1H), 5.91 (s, 2H), 4.94 (bs, 2H), 4.77 (bs, 2H), 4.01 (t, J = 7.1 Hz, 1H), 1.78 (m, 2H), 1.3 (m, 2H), 0.95 (t, J = 7.4 Hz, 1H).  | 39     |

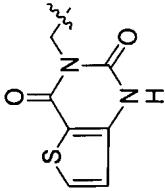
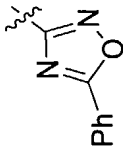
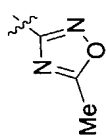
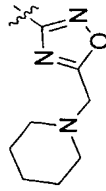
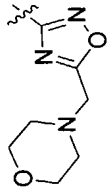
| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 190 | 331 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2-amino-9H-purin-6-ylamino)methyl]-benzamide                     | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.16 (s, 1H), 9.60 (br, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.62 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.20 (m, 2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H)  | 39   |
| 191 | 332 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2-chloro-9H-purin-6-ylamino)methyl]-benzamide                    | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6, J = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H)  | 39   |
| 192 | 333 |    | CH | CH | N-(2-Amino-phenyl)-4-[(9-butyl-2-chloro-9H-purin-6-ylamino)methyl]-benzamide            | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.60 (s, 1H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd, J = 6.7, 8.0 Hz, 2H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J=7.1 Hz, 3H)                       | 39   |
| 193 | 334 |    | CH | CH | N-(2-Amino-phenyl)-4-[(1H-benzimidazol-2-ylmethyl)-amino]-benzamide                     | <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 12.39 (bs, 1H), 9.32 (s, 1H), 7.81 (d, J=8.2 Hz, 2H), 7.56 (bs, 1H), 7.21-7.17 (m, 3H), 6.99-6.97 (m, 2H), 6.81 (d, J=8.2 Hz, 1H), 6.77 (d, J=8.8 Hz, 2H), 6.63 (t, J=7.0 Hz, 1H), 4.85 (s, 2H), 4.62 (d, J=5.3 Hz, 2H).   | 11   |
| 194 | 335 |  | CH | CH | N-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide | <sup>1</sup> H NMR: (CDCl <sub>3</sub> ) δ (ppm): 8.23 (dd, J = 7.8, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (td, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H). <b>MS:</b> (calc.) 414.2; (obt.) 415.3 (MH) <sup>+</sup> | 19   |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 195 | 336 |    | CH | CH | N-(2-Amino-phenyl)-4-(6-chloro-2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.69 (bs, 1H, NH), 8.71 (s, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.02 (td, J = 7.6, 1.5 Hz, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.64 (td, J = 7.6, 1.4 Hz, 1H), 5.34 (s, 2H), 4.94 (bs, 2H). <b>MS:</b> (calc.) 404.1; (obt.) 405.0 (MH) <sup>+</sup>   | 19   |
| 196 | 337 |    | CH | CH | N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide          | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H). <b>MS:</b> (calc.) 384.2; (obt.) 385.0 (MH) <sup>+</sup> | 19   |
| 197 | 338 |   | CH | CH | N-(2-Amino-phenyl)-4-(6,7-dimethoxy-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide     | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.62 (bs, 1H), 8.50 (s, 1H), 8.41 (d, J = 8.2 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.17 (s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.96 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.58 (dd, J = 6.9, 6.9 Hz, 1H), 5.26 (s, 2H), 4.88 (bs, 2H), 3.91 (s, 3H), 3.87 (s, 3H). <b>MS:</b> (calc.) 430.2; (obt.) 431.1 (MH) <sup>+</sup>   | 19   |
| 198 | 339 |  | CH | CH | N-(2-Amino-phenyl)-4-(6,7-difluoro-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide      | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.66 (bs, 1H), 8.69 (s, 1H), 8.07 (dd, J = 8.8, 10.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 14.3, 11.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.1, 1.2 Hz, 1), 6.58 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.28 (s, 2H), 4.89 (bs, 2H). <b>MS:</b> (calc.) 406.1; (obt.) 407.0 (MH) <sup>+</sup>   | 19   |

| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization  | Schm |
|-----|-----|---|----|----|--|---|------|
| 199 | 340 |    | CH | CH | N-(2-Amino-phenyl)-4-[1-(2-dimethylaminoethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide   | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 7.8, 1.2 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.22 (s, 2H), 4.88 (bs, 2H), 4.24 (t, J = 7.1 Hz, 2H), 2.5 (m, 2H) 2.22 (s, 6H). <b>MS:</b> (calc.) 457.2; (obt.) 458.1 (MH) <sup>+</sup>  | 19   |
| 200 | 341 |    | CH | CH | N-(2-Amino-phenyl)-4-[1-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.4, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.22 (s, 2H), 4.87 (bs, 2H), 4.28 (t, J = 6.7 Hz, 2H), 3.50 (t, J = 4.5 Hz, 4H), 2.58 (t, J = 6.7 Hz, 2H), 2.47-2.44 (m, 4H). <b>MS:</b> (calc.) 499.2; (obt.) 500.3 (MH) <sup>+</sup> | 19   |
| 201 | 342 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide                           | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.65 (bs, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.99 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.45 (s, 2H), 4.88 (bs, 2H). <b>MS:</b> (calc.) 462.1; (obt.) 463.1 (MH) <sup>+</sup>  | 19   |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 202 | 343 |    | CH | CH | N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide         | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). <b>MS:</b> (calc.) 392.1; (obt.) 393.0 (MH) <sup>+</sup> .  | 43   |
| 203 | 344 |    | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide     | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 9.1, 4.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.20 (s, 2H), 4.88 (bs, 2H) 4.14 (q, J = 7.0, 2H), 1.21 (t, J = 7.0, 3H). <b>MS:</b> (calc.) 492.1; (obt.) 493.0 (MH) <sup>+</sup> .  | 19   |
| 204 | 345 |   | CH | CH | N-(2-Amino-phenyl)-4-[1-(4-methoxybenzyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.62 (bs, 1H), 8.10 (dd, J = 7.7, 1.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.71 (ddd, J = 7.9, 7.9, 1.5 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 6.6 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.33 (s, 2H), 5.28 (s, 2H), 4.89 (bs, 2H), 3.71 (s, 3H). <b>MS:</b> (calc.) 506.2; (obt.) 507.1 (MH) <sup>+</sup> . | 19   |
| 205 | 346 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide                             | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.66 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.00 (dd, J = 8.7, 2.3 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.28 (s, 2H), 4.87 (bs, 2H). <b>MS:</b> (calc.) 448.0; (obt.) 449.0 (MH) <sup>+</sup> .   | 19   |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 206 | 347 |    | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-benzotriazin-3-ylmethyl)-benzamide   | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.63 (bs, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.8, 2.2 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.67 (s, 2H), 4.87 (bs, 2H). <b>MS:</b> (calc.) 449.0; (obt.) 450.0 (MH) <sup>+</sup> . | 19   |
| 207 | 348 |    | CH | CH | N-(2-Amino-phenyl)-4-(6-chloro-4-oxo-4H-benzotriazin-3-ylmethyl)-benzamide  | <sup>1</sup> H NMR: (DMSO) δ (ppm): 9.63 (bs, 1H), 8.30-8.24 (m, 2H), 8.15 (ddd, J = 8.6, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.67 (s, 2H), 4.88 (bs, 2H). <b>MS:</b> (calc.) 405.1; (obt.) 406.0 (MH) <sup>+</sup> .  | 19   |
| 208 | 349 |    | CH | CH | N-(2-Amino-phenyl)-4-[(3-fluoro-2-pyridinyl-amino)-methyl]-benzamide        | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.07 (bs, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.64-7.44 (m, 3H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.78 (bs, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.48 (dd, J = 8.1, 2.6 Hz, 1H), 6.16 (dd, J = 7.7, 2.5 Hz, 1H), 4.76-4.55 (m, 4H). HRMS (calc.): 336.1386, (found): 336.1389.                           | 11   |
| 209 | 350 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3,4,5-trifluoro-2-pyridinyl-amino)-methyl]-benzamide | <sup>1</sup> H NMR (acetone-d <sub>6</sub> ) δ (ppm): 9.06 (bs, 1H), AB system (δ <sub>A</sub> = 8.02, δ <sub>B</sub> = 7.56, J = 8.3 Hz, 4H), 7.74-7.65 (m, 1H), 7.33 (d, J = 8.0, 1H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.96-6.83 (m, 2H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 4.74 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H).   | 11   |

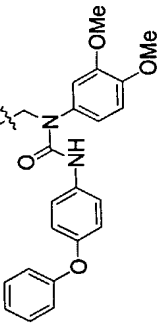
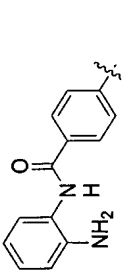
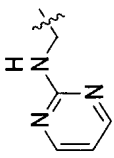
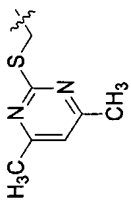
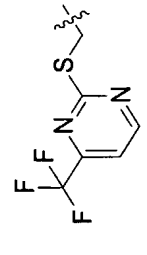
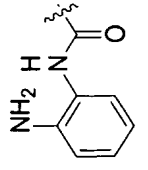
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 210 | 351 |    | CH | CH | N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-yl)methylbenzamide | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). <b>MS:</b> (calc.) 392.1; (obt.) 393.0 (MH) <sup>+</sup> . | 43   |
| 211 | 352 |    | CH | CH | N-(2-Amino-phenyl)-4-(5-phenyl-[1,2,4]oxadiazol-3-yl)methylbenzamide                       | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.85 (bs, 1H), 8.24-8.19 (m, 6H), 7.79-7.66 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.00 (dd, J = 7.3, 7.3 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.3, 7.3 Hz, 1H), 4.96 (bs, 2H). <b>MS:</b> (calc.) 356.1; (obt.) 357.0 (MH) <sup>+</sup> .  | 50   |
| 212 | 353 |    | CH | CH | N-(2-Amino-phenyl)-4-(5-methyl-[1,2,4]oxadiazol-3-yl)methylbenzamide                       | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.81 (bs, 1H), 8.17-8.11 (m, 4H), 7.18 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (bs, 2H), 2.70 (s, 3H). <b>MS:</b> (calc.) 294.1; (obt.) 295.0 (MH) <sup>+</sup> .   | 50   |
| 213 | 354 |   | CH | CH | N-(2-Amino-phenyl)-4-(5-piperidin-1-yl)methylbenzamide                                     | <b><sup>1</sup>H NMR: (acetone)</b> $\delta$ (ppm): 9.29 (bs, 1H), 8.21 (m, 4H), 7.31 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.68 (bs, 2H), 3.94 (s, 2H), 2.58 (t, J = 5.1 Hz), 1.63-1.55 (m, 4H), 1.47-1.43 (m, 2H). <b>MS</b> (Calc) 377.2; (Obt.) 378.3 (MH) <sup>+</sup> .   | 50   |
| 214 | 355 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-morpholin-4-yl)methylbenzamide                                     | <b><sup>1</sup>H NMR: (acetone)</b> $\delta$ (ppm): 9.28 (bs, 1H), 8.21 (m, 4H), 7.31 (d, J = 8.1 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.67 (bs, 2H), 4.01 (s, 2H), 3.66 (t, J = 4.8 Hz), 2.65 (t, J = 4.4 Hz). <b>MS:</b> (Calc.) 379.2; (Obt.): 380.2 (MH) <sup>+</sup> .                | 50   |

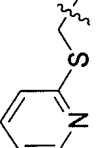
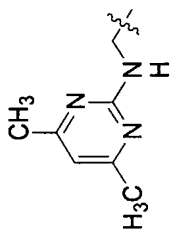
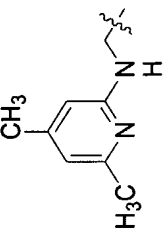
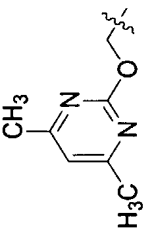
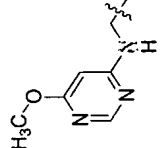


| Ex. | Cpd | W | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 215 | 356 |   | CH | CH | N-(2-Amino-phenyl)-4-(5-propyl-1,2,4-oxadiazol-3-ylmethyl)-benzamide                | <b><sup>1</sup>H NMR (DMSO)</b> δ (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.88 (s, 2H), 4.16 (s, 2H), 2.87 (t, 7.0, 2H), 1.72 (q, J = 7.5 Hz, 2H), 0.92 (t, J = 7.0 Hz, 3H). (MH) <sup>+</sup> : 337.2.   | 50   |
| 216 | 357 |   | CH | CH | N-(2-Amino-phenyl)-4-(5-pyridin-3-yl-1,2,4-oxadiazol-3-ylmethyl)-benzamide          | <b><sup>1</sup>H NMR (DMSO)</b> δ (ppm): 9.64 (s, 1H), 9.24 (d, J = 1.8 Hz, 1H); 8.86 (dd, J = 1.3 Hz, J = 4.8 Hz, 1H), 8.45 (dd, J = 1.8 Hz, J = 6.2 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.66 (dd, J = 4.8 Hz, J = 7.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.89 (s, 2H), 4.31 (s, 2H). (MH) <sup>+</sup> : 372.3. | 50   |
| 217 | 358 |   | CH | CH | N-(2-Amino-phenyl)-4-(5-pyridin-4-yl-1,2,4-oxadiazol-3-ylmethyl)-benzamide          | <b><sup>1</sup>H NMR (DMSO)</b> δ (ppm): 9.63 (s, 1H), 8.87 (d, J = 6.2 Hz, 2H); 7.95-8.02 (m, 3H), 7.50 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.33 (s, 2H). (MH) <sup>+</sup> : 372.3.   | 50   |
| 218 | 359 |   | CH | CH | 4-(5-Acetylamino-4-cyano-thiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide          | <b><sup>1</sup>H NMR (DMSO)</b> δ (ppm): 11.62 (s, 1H), 9.60 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.591 (dd, J = 7.7, 7.7 Hz, 1H), 4.89 (bs, 2H), 4.13 (s, 2H), 2.17 (s, 3H). LRMS: 390.1 (calc) 391.2 (found).  | 49   |
| 219 | 360 |   | CH | CH | 4-(5-Benzoylamino-4-cyano-3-methylthiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide | <b><sup>1</sup>H NMR (DMSO)</b> δ (ppm): 11.77 (s, 1H), 9.61 (s, 1H); 7.93 (d, J = 7.0 Hz, 4H), 7.52-7.63 (m, 3H), 7.38 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.89 (s, 2H), 4.15 (s, 2H), 2.24 (s, 3H). (MH) <sup>+</sup> : 467.0   | 49   |

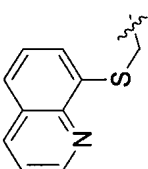
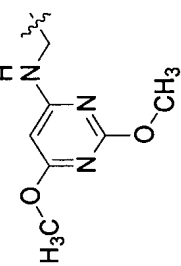
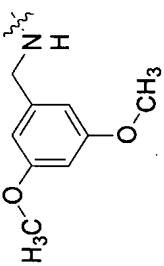
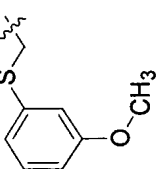
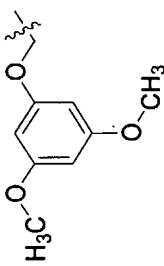
| Ex. | Cpd | W | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 220 | 361 |   | CH | CH | N-(2-Amino-phenyl)-4-(4-cyano-3-methyl-5-(3-phenylureido)-thiophen-2-ylmethyl)-benzamide | <b><sup>1</sup>H NMR (DMSO)</b> $\delta$ (ppm): 10.12 (s, 1H), 9.61 (s, 1H), 9.21 (s, 1H); 7.93 (d, J = 7.6 Hz, 2H), 7.27-7.43 (m, 6H), 7.16 (d, J = 7.6 Hz, 1H), 6.93-7.05 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H), 4.08 (s, 2H), 2.19 (s, 3H). (MH) <sup>+</sup> : 482.4   | 49   |
| 221 | 362 |   | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamide           | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.60 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92-7.04 (m, 5H), 6.75 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 6.57 (td, J = 7.4 Hz, 1.4 Hz, 1H), 5.24 (s, 2H), 4.88 (bs, 2H); 4.82 (s, 2H). (MH) <sup>+</sup> : 374.1   | 11   |
| 222 | 363 |   | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-ylmethyl)-benzamide          | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.58 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.19-7.11 (m, 3H), 7.04-6.92 (m, 2H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (td, J = 8.0 Hz, 1.6 Hz, 1H), 5.31 (s, 2H); 4.88 (bs, 2H); 3.70 (s, 2H). (MH) <sup>+</sup> : 390.1                               | 11   |
| 223 | 364 |   | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-ylmethyl)-benzamide   | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.57 (bs, 1H), 7.98 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.45-7.40 (m, 3H), 7.15 (d, J = 8.2 Hz, 1H), 7.09-7.05 (m, 1H), 6.96 (dd, J = 7.6, 7.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 7.6, 7.6 Hz, 1H), 5.31 (s, 2H), 4.90 (bs, 2H), 4.87 (s, 2H). (MH) <sup>+</sup> : 375.1                       | 11   |
| 224 | 365 |   | CH | CH | N-(2-Amino-phenyl)-4-(1-hydroxy-3-oxo-indan-2-ylmethyl)-benzamide                        | <b><sup>1</sup>H NMR: (DMSO)</b> $\delta$ (ppm): 9.67 (s, 1H); 7.98 (d, J = 8.2 Hz, 2H), 7.73-7.84 (m, 3H), 7.53-7.62 (m, 3H), 7.24 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 5.27 (t, J = 6.4 Hz, 1H), 4.95 (s, 2H), 3.21-3.30 (m, 1H), 3.11-3.13 (m, 2H). (MH) <sup>+</sup> : 373.1 | 46   |

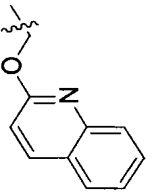
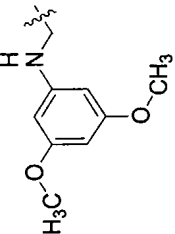
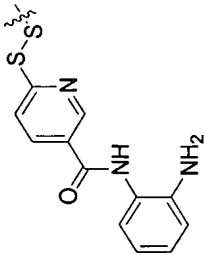
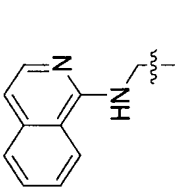
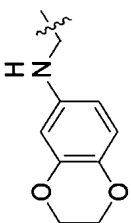
| Ex. | Cpd | W | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 225 | 366 |   | CH | CH | N-(2-Amino-phenyl)-4-phenoxybenzamide  | <sup>1</sup> H NMR (DMSO) δ (ppm): 9.61 (s, 1H); 8.01 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.06-7.24 (m, 6H), 6.97 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H). (MH) <sup>+</sup> : 305.0  | 1    |
| 226 | 367 |   | CH | CH | N-(2-Amino-phenyl)-4-[5-(4-methoxyphenyl)-2,5-dihydro-furan-2-yl]-benzamide              | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.77 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38-6.98 (m, 6H), 6.91 (d, J = 8.4 Hz, 2H), 6.09-5.98 (m, 4H), 3.81 (s, 3H).   | 52   |
| 230 | 371 |   | CH | CH | N-(2-Amino-phenyl)-4-[1,3-bis(3,4-dimethoxyphenyl)-ureidomethyl]-benzamide               | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.08 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.70 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39-7.33 (m, 1H), 7.30-6.90 (m, 7H), 6.87 (dd, J = 2.2, 8.35 Hz, 1H), 6.78 (dd, J = 2.2, 8.35 Hz, 1H), 5.01 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H). | 57   |
| 231 | 372 |   | CH | CH | N-(2-Amino-phenyl)-4-[3-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-ureidomethyl]-benzamide | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.02 (brs, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.42-7.24 (m, 6H), 7.16 (t, J = 7.5 Hz, 1H), 6.91 (brd, J = 5.71 Hz, 3H), 6.75 (brd, J = 8.3 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 4.99 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H).         | 57   |
| 232 | 373 |   | CH | CH | N-(2-Amino-phenyl)-4-[1-(3,4-dimethoxyphenyl)-3-phenyl-ureidomethyl]-benzamide           | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.10 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.80-7.72 (m, 1H), 7.50 (dd, J = 7.0, 5.7 Hz, 4H), 7.37 (d, J = 7.9 Hz, 1H), 7.30-6.94 (m, 7H), 6.78 (d, J = 6.6 Hz, 1H), 5.03 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H).                        | 57   |

| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 233 | 374 |    | CH | CH | N-(2-Amino-phenyl)-4-[(1-{3,4-dimethoxy-phenyl}-3-(4-phenoxy-phenyl)-ureidomethyl)-benzamide | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 8.02 (brs, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 8.35 Hz, 2H), 7.43-7.32 (m, 5H), 7.10-7.30 (2m, 5H), 7.19-7.10 (m, 2H), 7.01 (dd, J = 8.35, 2.2 Hz, 3H), 6.94 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.34 (s, 2H), 5.02 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H). | 57   |
| 234 | 375 |    | CH | CH | Biphenyl-4,4'-dicarboxylic acid bis-[(2-amino-phenyl)-amide]                                 | <sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 9.80 (bs, 2H), 8.16 (d, J=7.9 Hz, 4H), 7.96 (d, J= 7.9 Hz, 4H), 7.23 (d, J=7.4 Hz, 2H), 7.03 (dd, J=6.9, 7.4 Hz, 2H), 6.84 (d, J=8.2 Hz, 2H), 6.66 (dd, J=6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).  | 15   |
| 236 | 377 |    | CH | CH | N-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide                                   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.6 (bs, 1H), 8.32 (d, J=4.9 Hz, 2H), 7.97 (dt, J= 7.9, 9.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47 (d, J=8.2 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.01 (dt, J=7.4, 7.7 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).  | 13   |
| 237 | 378 |    | CH | CH | N-(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide                   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.61 (d, J= 7.9 Hz, 2H), 7.21 (d, J=7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J=7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).   | 11   |
| 238 | 379 |  | CH | CH | N-(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 9.07 (d, J=5.2 Hz, 1H), 7.97 (d, J=7.4 Hz, 2H), 7.78 (d, J=4.7 Hz, 1H), 7.63 (d, J=7.4 Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.01 (dt, J= 7.4, 7.7 Hz, 1H), 6.81 (d, J=8.2 Hz, 1H), 6.64 (dt, J=7.1, 7.4 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H).   | 11   |
| 239 | 380 |  | N  | CH | Pyridine-2,5-dicarboxylic acid bis-[(2-amino-phenyl)-amide]                                  | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 10.23 (bs, 1H), 10.04 (bs, 1H), 9.30 (s, 1H), 8.62 (dd, J=1.8, 8.0 Hz, 1H), 8.30 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.4 Hz, 1H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=7.0, 14.0 Hz, 2H), 6.90-6.83 (m, 2H), 6.74-6.63 (m, 2H), 5.11 (bs, 4H).  | 1    |

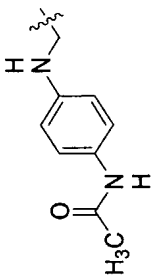
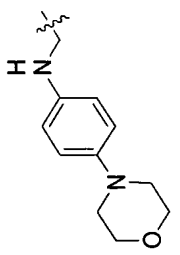
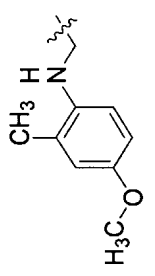
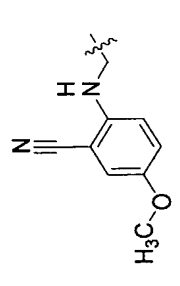
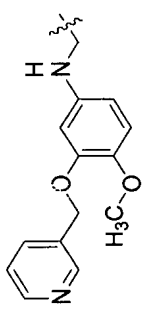
| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization  | Schm |
|-----|-----|---|----|----|---|---|------|
| 240 | 381 |    | CH | CH | N-(2-Amino-phenyl)-4-(pyridin-2-ylsulfanylmethyl)-benzamide               | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 8.52 (bs, 1H), 7.96 (d, J=7.4 Hz, 2H), 7.69 (d, J=5.8 Hz, 1H), 7.59 (d, J=7.4 Hz, 2H), 7.38 (d, J=7.7 Hz, 1H), 7.19 (bs, 2H), 7.00 (d, J=6.9 Hz, 1H), 6.83 (d, J=6.9 Hz, 1H), 6.64 (dd, J=6.7, 7.2 Hz, 1H), 4.94 (bs, 2H), 4.55 (b+s, 2H). | 11   |
| 241 | 382 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dimethyl-pyrimidin-2-ylamino)methyl]-benzamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.65 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.57 (d, J=6.3 Hz, 1H), 7.47 (d, J=7.7 Hz, 2H), 7.21 (d, J=7.4 Hz, 1H), 7.00 (d, J=5.8 Hz, 1H), 6.59 (d, J=6.6 Hz, 1H), 6.64 (dd, J=6.0, 7.4 Hz, 1H), 5.01 (s, 2H), 4.61 (d, J=6.0 Hz, 2H), 2.24 (s, 6H).          | 33   |
| 242 | 383 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dimethyl-pyridin-2-ylamino)methyl]-benzamide   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.50 (d, J=8.2 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.01 (dd, J=7.7, 7.4 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.33 (s, 1H), 6.25 (s, 1H), 4.58 (d, J=4.4 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H).      | 33   |
| 243 | 384 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dimethyl-pyrimidin-2-ylloxymethyl)-benzamide   | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.58 (bs, 1H), 7.88 (d, J=5.8 Hz, 2H), 7.46 (d, J=8.2 Hz, 2H), 6.90-6.81 (m, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.50 (t, J=7.4 Hz, 1H), 6.40-6.38 (m, 1H), 6.29-6.26 (m, 1H), 5.33 (s, 2H), 2.25 (s, 6H).   | 11   |
| 244 | 385 |  | CH | CH | N-(2-Amino-phenyl)-4-[(6-methoxypyrimidin-4-ylamino)methyl]-benzamide     | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.64 (bs, 1H), 8.21 (bs, 1H), 7.95 (d, J=7.96 Hz, 2H), 7.83 (d, J=5.8 Hz, 1H), 7.44 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.00 (dd, J=7.4, 7.7 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.64 (d, J=7.1 Hz, 1H), 4.96 (bs, 2H), 4.58 (bs, 2H), 3.81 (s, 3H).  | 33   |

| Ex. | Cpd | W | Y  | Z  | Name   | Characterization  | Schm |
|-----|-----|---|----|----|--|---|------|
| 245 | 386 |   | CH | CH | 4-[(6-Acetyl-benzo[1,3]dioxol-5-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.79 (bs, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.96 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4 Hz, 1H), 7.02 (dd, J=7.1, 7.7 Hz, 1H), 6.83 (d, J=7.7 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.59 (bs, 2H), 2.52 (bs, 3H).                             | 33   |
| 246 | 387 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-methoxy-pyrimidin-2-ylamino)-methyl]-benzamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.47 (bs, 2H), 7.39 (bs, 1H), 7.19 (d, J=7.4 Hz, 1H), 7.00 (dd, J=6.9, 7.4 Hz, 1H), 6.81 (d, J=7.1 Hz, 1H), 6.63 (dd, J=7.7, 6.8 Hz, 1H), 6.10 (bs, 1H), 4.56 (d, J=6.0 Hz, 2H), 3.83 (s, 3H).   | 33   |
| 247 | 388 |   | CH | CH | N-(2-Amino-phenyl)-4-[(2,6-dimethoxy-pyridin-3-ylamino)-methyl]-benzamide        | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.63 (bs, 1H), 7.94 (d, J=6.9 Hz, 2H), 7.47 (d, J=6.59 Hz, 2H), 7.15 (d, J=7.9 Hz, 1H), 6.99 (dd, J=5.7, 7.4 Hz, 1H), 6.80 (d, J=7.8 Hz, 1H), 6.71 (d, J=6.6 Hz, 1H), 6.62 (dd, J=7.7, 7.1 Hz, 1H), 6.15 (d, J=8.2 Hz, 1H), 4.96 (bs, 2H), 4.38 (bs, 2H), 3.94 (s, 3H), 3.75 (s, 3H). | 33   |
| 248 | 389 |   | CH | CH | N-(2-Amino-phenyl)-4-[(1H-benzimidazol-2-ylamino)-methyl]-benzamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 10.9 (bs, 1H), 9.64 (bs, 1H), 7.99 (bs, 2H), 7.55 (bs, 2H), 7.21-7.17 (m, 3H), 7.14-6.81 (m, 4H), 6.64 (d, J=6.0 Hz, 1H), 4.92 (bs, 2H), 4.65 (bs, 2H).   | 33   |
| 249 | 390 |   | CH | CH | N-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-2-ylamino)-methyl]-benzamide            | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.60 (bs, 1H), 7.96 (d, J=7.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.37-7.30 (m, 1H), 7.25-7.21 (m, 2H), 7.19-6.99 (m, 1H), 6.84-6.81 (m, 1H), 6.67-6.64 (m, 1H), 6.11-6.07 (m, 1H), 5.93-5.89 (m, 1H), 4.93 (bs, 2H), 4.56 (d, J=5.8 Hz, 2H), 3.80 (s, 3H).                                   | 37   |

| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization  | Schm |
|-----|-----|---|----|----|--|---|------|
| 250 | 391 |    | CH | CH | N-(2-Amino-phenyl)-4-(quinolin-8-ylsulfanylmethyl)-benzamide               | <sup>1</sup> H-NMR (DMSO-d6), δ (ppm): 9.68 (bs, 1H), 8.95 (bs, 2H), 8.43-8.38 (m, 1H), 7.90 (bs, 2H), 7.80-7.55 (m, 6H), 7.22 (d, J= 7.7 Hz, 1H), 7.03 (d, J= 7.7 Hz, 1H), 6.63 (d, J=7.4 Hz, 1H), 5.05 (bs, 2H), 4.48 (d, J=7.7, 2H).   | 11   |
| 251 | 392 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2,6-dimethoxypyrimidin-4-ylamino)-methyl]-benzamide | <sup>1</sup> H-NMR (DMSO-d6), δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.84 (t, J=5.9 Hz, 1H), 7.46 (d, J=7.46 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.04 (d, J=6.6 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.64 (dd, J=7.7, 7.4 Hz, 1H), 5.51 (bs, 1H), 4.57 (bs, 2H), 3.82 (s, 3H), 3.84 (s, 3H).       | 37   |
| 252 | 393 |    | CH | CH | N-(2-Amino-phenyl)-4-(3,5-dimethoxybenzylamino)-benzamide                  | <sup>1</sup> H-NMR (DMSO-d6), δ (ppm): 9.63 (bs, 1H), 7.79 (d, J=8.5 Hz, 2H), 7.19 (d, J=6.6 Hz, 1H), 7.00 (dd, J=7.9, 7.1 Hz, 1H), 6.62 (t, J=6.0 Hz, 1H), 6.82 (dd, J=1.4, 7.9 Hz, 1H), 6.67 (d, J= 8.8 Hz, 2H), 6.58 (bs, 2H), 6.42 (bs, 1H), 4.87 (bs, 2H), 4.34 (d, J=6.0 Hz, 2H), 3.77 (s, 6H). | 37   |
| 253 | 394 |   | CH | CH | N-(2-Amino-phenyl)-4-(3-methoxyphenylsulfanylmethyl)-benzamide             | <sup>1</sup> H-NMR (DMSO-d6), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.29-7.20 (m, 2H), 7.02-6.95 (m, 2H), 6.84-6.79 (m, 1H), 6.67-6.62 (m, 1H), 6.57-6.54 (m, 1H), 6.44-6.41 (m, 1H), 4.93 (bs, 2H), 4.41 (bs, 2H), 3.79 (s, 3H).                                   | 11   |
| 254 | 395 |  | CH | CH | N-(2-Amino-phenyl)-4-(3,5-dimethoxyphenoxy-methyl)-benzamide               | <sup>1</sup> H-NMR (DMSO-d6), δ (ppm): 9.72 (bs, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=6.9, 7.1 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (dd, J= 7.4, 7.7 Hz, 1H), 6.27 (s, 2H), 6.26 (s, 1H), 5.23 (s, 2H), 5.21 (bs, 2H), 3.77 (s, 6H).             | 11   |

| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization  | Schm |
|-----|-----|---|----|----|--|---|------|
| 255 | 396 |    | CH | CH | N(2-Amino-phenyl)-4-(quinolin-2-yl)oxymethylbenzamide                        | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.70 (bs, 1H), 8.35 (d, J=9.1 Hz, 2H), 8.05 (d, J=7.9 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.76-7.69 (m, 2H), 7.51 (dd, J=6.9, 7.1 Hz, 1H), 7.24-7.16 (m, 2H), 7.02 (dd, J=6.9, 7.4 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.4 Hz, 1H), 5.66 (s, 2H), 4.94 (bs, 2H). | 11   |
| 256 | 397 |    | CH | CH | N(2-Amino-phenyl)-4-[(3,5-dimethoxyphenylamino)methyl]benzamide              | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.62 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.49 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 7.00 (dd, J=7.5, 7.9 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 6.63 (dd, J=7.0, 8.0 Hz, 1H), 5.78 (s, 2H), 5.76 (s, 1H), 4.92 (bs, 2H), 4.35 (d, J=5.7, 2H), 3.65 (s, 6H).                                      | 33   |
| 257 | 398 |    | CH | N  | bis(N(2-Amino-phenyl)-4-[(nicotinamide)-6-disulfide])                        | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.82 (bs, 2H), 9.08 (bs, 2H), 8.34 (d, J=8.3 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 7.01 (dd, J=6.3, 7.0 Hz, 2H), 6.80 (d, J=7.9 Hz, 2H), 6.61 (t, J=7.03 Hz, 2H), 5.05 (bs, 4H).   | 1    |
| 258 | 399 |   | CH | CH | N(2-Amino-phenyl)-4-[(isoquinolin-1-ylaminomethyl)]benzamide                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.90 (bs, 1H), 8.16 (bs, 2H), 7.65 (d, J=4.8 Hz, 2H), 7.54 (bs, 2H), 7.25 (d, J=7.0 Hz, 2H), 7.11 (bs, 2H), 7.07-7.02 (m, 2H), 6.84 (d, J=7.9 Hz, 1H), 6.67 (bs, 1H), 5.01 (bs, 2H), 4.88 (bs, 2H).   | 33   |
| 259 | 400 |  | CH | CH | N(2-Amino-phenyl)-4-[(2,3-dihydrobenzo[1,4]dioxin-6-ylaminomethyl)]benzamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.0 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.22 (d, J=7.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.84 (bs, 1H), 6.82-6.71 (m, 2H), 6.16 (d, J=6.6 Hz, 1H), 6.08 (s, 1H), 4.32 (bs, 2H), 4.16-4.13 (m, 4H).   | 33   |

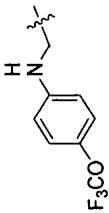
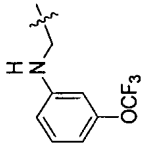
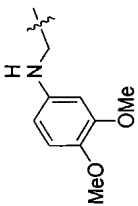
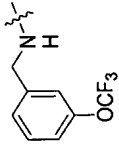
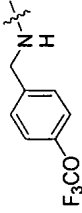


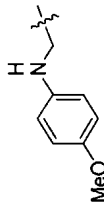
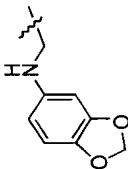
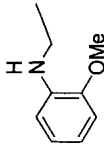
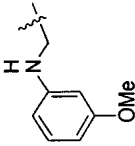
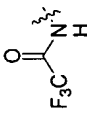
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 260 | 401 |    | CH | CH | 4-[(4-Acetylamino-phenylamino)-methyl]-N(2-amino-phenyl)-benzamide                     | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.66 (bs, 1H), 9.56 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.53 (d, J=7.9 Hz, 2H), 7.28 (d, J=8.8 Hz, 2H), 7.22 (d, J=7.9 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.65 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.3 Hz, 2H), 4.98 (bs, 2H), 4.38 (bs, 2H), 2.00 (s, 3H).  | 33   |
| 261 | 402 |    | CH | CH | N(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide                  | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.5 Hz, 1H), 7.02 (dd, J=7.0, 7.9 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.78 (d, J=8.8 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.8 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 3.74 (t, J=4.4 Hz, 4H), 2.92 (t, J=4.4 Hz, 4H).                                  | 33   |
| 262 | 403 |    | CH | CH | N(2-Amino-phenyl)-4-[(4-methoxy-2-methyl-phenylamino)-methyl]-benzamide                | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.64 (bs, 1H), 7.96 (d, J=7.6 Hz, 2H), 7.52 (d, J=7.6 Hz, 2H), 7.21 (d, J=8.2 Hz, 1H), 7.02 (t, J=8.2, 7.0 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.71-6.53 (m, 3H), 6.32-6.30 (m, 1H), 4.94 (bs, 2H), 4.45 (d, J=5.9 Hz, 2H), 3.65 (s, 3H), 2.23 (s, 3H).   | 33   |
| 263 | 404 |   | CH | CH | N(2-Amino-phenyl)-4-[(2-cyano-4-methoxy-phenylamino)-methyl]-benzamide                 | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.4 Hz, 2H), 7.56 (d, J=7.5 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 6.99 (d, J=7.5 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.63 (t, J=6.6 Hz, 2H), 6.27 (s, 1H), 4.93 (bs, 2H), 4.55 (d, J=5.3 Hz, 2H), 3.69 (s, 6H).  | 33   |
| 264 | 405 |  | CH | CH | N(2-Amino-phenyl)-4-[(4-methoxy-3-(pyridin-3-ylmethoxy)-phenylamino)-methyl]-benzamide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.62 (s, 1H), 8.72 (s, 1H), 8.49 (d, J=10.1 Hz, 1H), 7.93 (d, J=7.9 Hz, 2H), 7.68 (d, J=6.6 Hz, 1H), 7.37 (d, J=7.5 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.78 (d, J=7.9 Hz, 1H), 6.69 (d, J=8.8 Hz, 1H), 6.62 (d, J=7.5 Hz, 1H), 6.23 (d, J=2.6 Hz, 1H), 6.09 (J=8.8 Hz, 1H), 5.76 (s, 1H), 4.64 (bs, 4H), 3.62 (s, 3H). | 33   |

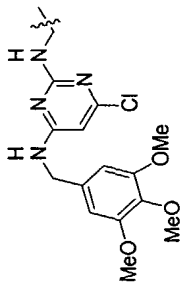
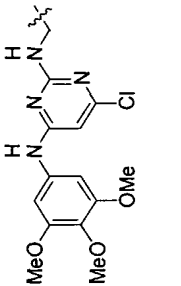
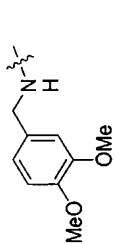
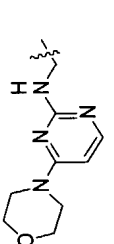
| Ex. | Cpd | W | Y  | Z  | Name   | Characterization  | Schm      |
|-----|-----|---|----|----|--|---|-----------|
| 265 | 406 |   | CH | CH | 2-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-4,5-dimethoxybenzoic acid                | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.67 (bs, 1H), 8.00 (d, J=7.9 Hz, 2H), 7.54 (d, J=7.9 Hz, 2H), 7.34 (s, 1H), 7.20 (d, J=7.9 Hz, 2H), 7.0 (t, J=7.9 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.62 (t, J=7.9 Hz, 1H), 6.31 (s, 1H), 4.95 (bs, 2H), 4.62 (bs, 2H), 3.75 (s, 3H), 3.70 (s, 3H).   | 33        |
| 266 | 407 |   | CH | CH | N-(2-Amino-phenyl)-4-[(3,5-dimethylphenylamino)methyl]benzamide                      | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.60 (s, 1H), 7.93 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.9 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.78 (d, J=7.9 Hz, 1H), 6.58 (t, J=7.0 Hz, 1H), 6.19-6.17 (m, 3H), 4.88 (s, 2H), 4.32 (d, J=5.7 Hz, 2H), 2.10 (s, 6H).  | 33        |
| 267 | 408 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4-pyridin-3-ylmethoxy)phenylamino]methylbenzamide             | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.65 (s, 1H), 8.72 (s, 1H), 8.54 (s, 1H), 8.49 (d, J=10.9 Hz, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.71 (d, J=7.9 Hz, 1H), 7.44 (d, J=8.3 Hz, 2H), 7.41-7.36 (m, 1H), 7.20 (d, J=7.9 Hz, 1H), 7.00 (t, J=7.4 Hz, 1H), 6.83 (d, J=7.0 Hz, 1H), 6.70-6.60 (m, 4H), 4.62 (s, 4H).                                  | 33        |
| 268 | 409 |   | CH | CH | N-(2-Amino-phenyl)-4-[(2,4-dimethylphenylamino)methyl]benzamide                      | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ), δ (ppm): 9.58 (s, 1H), 7.90 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.5 Hz, 2H), 7.15 (d, J=7.5 Hz, 1H), 6.96 (t, J=7.5 Hz, 1H), 6.79 (s, 1H), 6.76 (d, J=9.6 Hz, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.59 (t, J=7.0 Hz, 1H), 6.22 (d, J=7.9 Hz, 1H), 4.89 (bs, 2H), 4.39 (d, J=5.7 Hz, 2H), 2.15 (s, 3H), 2.10 (s, 3H).          | 33        |
| 269 | 410 |   | CH | CH | N-(2-Amino-phenyl)-4-[(2,4,6-trimethylphenylamino)methyl]benzamide                   | <sup>1</sup> H-NMR (CD <sub>3</sub> OD), δ (ppm): 7.91 (d, J=7.9 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.18 (d, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.92 (d, J=7.9 Hz, 1H), 6.77 (s, 3H), 4.15 (bs, 2H), 2.19 (s, 9H).  | 33        |
| 270 | 411 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-morpholin-4-yl)pyrimidin-2-ylamino]methylbenzamide | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ), δ *** (ppm): 9.66 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.82 (m, 1H), 7.47 (d, J=7.7 Hz, 2H), 7.21 (d, J=8.2 Hz, 1H), 7.03 (dd, J=7.1, 7.1 Hz, 1H), 6.84 (d, J=7.7 Hz, 1H), 6.65 (dd, J=7.4, 7.4 Hz, 1H), 6.17 (bs, 1H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.53 (d, J=5.8 Hz, 2H), 3.58 (m, 4H), 3.62 (m, 4H). | 24,<br>33 |

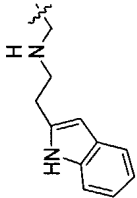
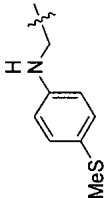
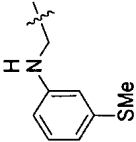
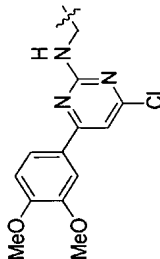
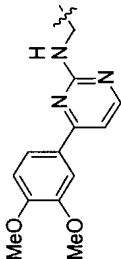
| Ex. | Cpd | W | Y  | Z  | Name  | Characterization  | Schm |
|-----|-----|---|----|----|---|---|------|
| 271 | 412 |   | CH | CH | N-(2-Amino-phenyl)-<br>4-(3,4,5-<br>trimethoxy-<br>benzylamino)-<br>benzamide | <sup>1</sup> H NMR (300 MHz, <b>DMSO-d<sub>6</sub></b> ) δ (ppm): 9.33 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.99 (m, 1H), 6.87 (dd, J = 6.0, 5.8 Hz, 1H), 6.82 (m, 1H), 6.77 (s, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.64 (m, 1H), 4.87 (s, 2H, NH <sub>2</sub> ), 4.32 (d, J = 5.5 Hz, 2H), 3.81 (s, 6H), 3.79 (s, 3H).   | 33   |
| 272 | 413 |   | CH | CH | N-(2-Amino-phenyl)-<br>4-(4-fluoro-<br>benzylamino)-<br>benzamide             | <sup>1</sup> H NMR (300 MHz, <b>DMSO-d<sub>6</sub></b> ) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.45 (dd, J = 5.8, 8.5 Hz, 2H), 7.21 (m, 3H), 6.91 (m, 2H), 6.81 (dd, J = 1.1, 8.0 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.62 (dd, J = 1.0, 7.2 Hz, 1H), 4.86 (s, 2H, NH <sub>2</sub> ), 4.39 (d, J = 6.0 Hz, 2H).   | 33   |
| 273 | 414 |   | CH | CH | N-(2-Amino-phenyl)-<br>4-(4-methoxy-<br>benzylamino)-<br>benzamide            | <sup>1</sup> H NMR (300 MHz, <b>DMSO-d<sub>6</sub></b> ) δ (ppm): 9.31 (s, 1H), 7.79 (dd, J = 1.1, 8.5 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.97 (m, 3H), 6.84 (m, 2H), 6.65 (m, 3H), 4.86 (s, 2H, NH <sub>2</sub> ), 4.33 (d, J = 5.5 Hz, 2H), 3.58 (d, J = 1.6 Hz, 3H).   | 33   |
| 274 | 415 |   | CH | CH | N-(2-Amino-phenyl)-<br>4-[(4-fluoro-<br>phenylamino)-<br>methyl]-benzamide    | <sup>1</sup> H NMR (300 MHz, <b>DMSO-d<sub>6</sub></b> ) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (ddd, J = 1.6, 7.1, 8.2 Hz, 1H), 6.93 (dd, J = 8.8, 9 Hz, 2H), 6.83 (dd, J = 1.1, 8.0 Hz, 1H), 6.63 (m, 3H), 6.35 (t, J = 6.2 Hz, 1H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.38 (d, J = 6.3 Hz, 2H).                 | 33   |
| 275 | 416 |   | CH | CH | N-(2-Amino-phenyl)-<br>4-(3-fluoro-<br>benzylamino)-<br>benzamide             | <sup>1</sup> H NMR (300 MHz, <b>DMSO-d<sub>6</sub></b> ) δ (ppm): 9.32 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.44 (m, 1H), 7.26 (m, 1H), 7.18 (dd, J = 1.4, 8.0 Hz, 2H), 7.12 (ddd, J = 1.7, 8.0, 8.2 Hz, 1H), 6.99 (m, 2H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.67 (dd, J = 1.6, 8.8 Hz, 2H), 6.62 (dd, J = 1.4, 7.4 Hz, 1H), 4.87 (s, 2H, NH <sub>2</sub> ), 4.45 (d, J = 6.0 Hz, 2H). | 33   |

| Ex. | Cpd | W | Y  | Z  | Name  | Characterization  | Schm      |
|-----|-----|---|----|----|---|---|-----------|
| 276 | 417 |   | CH | CH | N-(2-Amino-phenyl)-4-[(3-fluorophenylamino)-methyl]-benzamide   | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 6.99-7.14 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.76 (m, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.34 (m, 2H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.41 (d, J = 6.0 Hz, 2H).  | 33        |
| 277 | 418 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-methyl-pyrimidin-2-ylamino)-methyl]-benzamide                       | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 8.23 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (ddd, J = 1.5, 7.1, 8.0 Hz, 1H), 6.83 (dd, J = 1.5, 8.1 Hz, 1H), 6.65 (m, 2H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.61 (m, 2H), 2.32 (s, 3H).   | 33        |
| 278 | 419 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dichloro-pyrimidin-2-ylamino)-methyl]-benzamide                            | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 8.82 (m, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 7.0 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.67 (m, 1H), 5.0 (bs, 2H, NH <sub>2</sub> ), 4.60 (d, J = 6.3 Hz, 2H).  | 33        |
| 279 | 420 |   | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-[(pyridin-3-ylmethyl)-amino]-pyrimidin-2-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.87 (s, 1H), 8.49 (bs, 2H), 7.26-8.02 (bm, 8H), 7.22 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.4, 7.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.1, 8.0 Hz, 1H), 5.86 (bs, 1H), 4.95 (s, 2H, NH <sub>2</sub> ), 4.51 (m, 2H).   | 24,<br>33 |
| 280 | 421 |   | CH | CH | N-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-3-ylamino)-methyl]-benzamide                                 | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 7.9 Hz, 1H), 7.12 (dd, J = 3.08 Hz, 8.79 Hz, 1H), 7.02 (dd, J = 7.0 Hz, 7.5 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (m, 2H), 6.15 (t, J = 6.16 Hz, 1H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.39 (d, J = 6.15 Hz, 2H), 3.75 (s, 3H). | 33        |

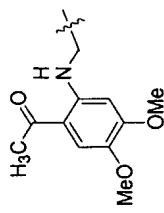
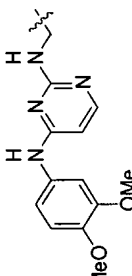
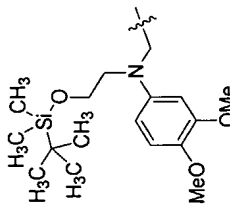
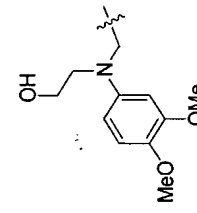
| Ex.  | Cpd  | W   | Y  | Z  | Name   | Characterization   | Schm |
|------|------|---|----|----|--|--|------|
| 281  | 422  |    | CH | CH | N-(2-Amino-phenyl)-4-((4-trifluoromethoxy-phenylamino)-methyl)-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 9.1 Hz, 2H), 7.03 (dd, J = 7.1, 8.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.71 (t, J = 6.0 Hz, 1H), 6.63-6.67 (m, 3H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.42 (d, J = 6.0 Hz, 2H).   | 33   |
| 282  | 423  |    | CH | CH | N-(2-Amino-phenyl)-4-((3-trifluoromethoxy-phenylamino)-methyl)-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.67 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.19 (m, 2H), 7.03 (ddd, J = 1.5, 8.0, 8.8 Hz, 1H), 6.85 (m, 2H), 6.63 (m, 2H), 6.55 (s, 1H), 6.50 (m, 1H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.44 (d, J = 6.0 Hz, 2H).  | 33   |
| 283a | 424b |    | CH | CH | N-(2-Amino-phenyl)-4-((3,4-dimethoxy-phenylamino)-methyl)-benzamide      | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.49 Hz, 7.49 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H). | 33   |
| 284  | 425  |   | CH | CH | N-(2-Amino-phenyl)-4-((3-trifluoromethoxy-benzylamino)-benzamide         | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.31 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.45-7.56 (m, 2H), 7.39 (s, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 6.96-7.03 (m, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 4.86 (s, 2H, NH <sub>2</sub> ), 4.48 (d, J = 5.8 Hz, 2H).  | 33   |
| 285  | 426  |  | CH | CH | N-(2-Amino-phenyl)-4-((3-trifluoromethoxy-benzylamino)-benzamide         | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 1.4, 7.7 Hz, 1H), 6.99 (ddd, J = 1.4, 8.0, 8.5 Hz, 2H), 6.81 (dd, J = 1.4, 8.0, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.85 (s, 2H, NH <sub>2</sub> ), 4.45 (d, J = 6.0 Hz, 2H).   | 33   |

| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm |
|-----|-----|---|----|----|--|--|------|
| 286 | 427 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4-methoxyphenylamino)methyl]benzamide     | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.64 (s, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 1.4, 8.0 Hz, 1H), 7.02 (ddd, J = 1.4, 7.4, 8.0 Hz, 1H), 6.83 (dd, J = 1.4, 8.0 Hz, 1H), 6.74 (m, 2H), 6.65 (ddd, J = 1.4, 7.7, 8.8 Hz, 1H), 6.58 (m, 2H), 5.99 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.36 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H). | 33   |
| 287 | 428 |    | CH | CH | N-(2-Amino-phenyl)-4-(benzo[1,3]dioxol-5-ylaminomethyl)benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.63-6.69 (m, 2H), 6.33 (d, J = 2.2 Hz, 1H), 6.15 (t, J = 6.16 Hz, 1H), 6.04 (dd, J = 2.2, 8.4 Hz, 1H), 5.86 (s, 2H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.35 (d, J = 6.16 Hz, 2H).     | 33   |
| 288 | 429 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2-methoxyphenylamino)methyl]benzamide     | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.63 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (ddd, J = 1.4, 7.1, 8.0 Hz, 1H), 6.86 (m, 2H), 6.56-6.75 (m, 3H), 6.43 (dd, J = 1.6, 7.7 Hz, 1H), 5.75 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.47 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H).                                       | 33   |
| 289 | 430 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-methoxyphenylamino)methyl]benzamide     | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.61 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (dd, J = 1.1, 7.7 Hz, 1H), 6.97-7.05 (m, 2H), 6.82 (dd, J = 1.2, 8.1 Hz, 1H), 6.46 (ddd, J = 1.4, 7.7, 8.0 Hz, 1H), 6.41 (t, J = 6.3 Hz, 1H), 6.16-6.25 (m, 3H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H).                            | 33   |
| 290 | 431 |  | CH | CH | N-(2-Amino-phenyl)-4-(2,2,2-trifluoroacetylaminomethyl)benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 11.53 (s, 1H), 9.71 (s, 1H), 8.08 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.0, 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.0, 7.6 Hz, 1H), 4.96 (s, 2H, NH <sub>2</sub> ).   | 14   |

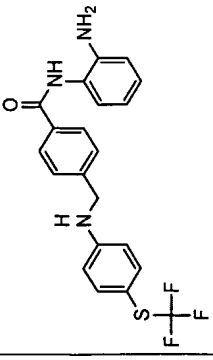
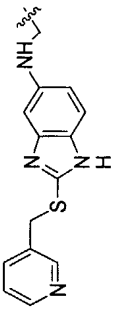
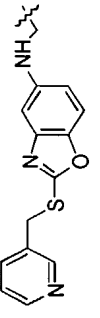
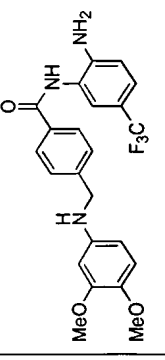
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization   | Schm         |
|-----|-----|---|----|----|--|--|--------------|
| 291 | 432 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-(3,4,5-trimethoxybenzylamino)-pyrimidin-2-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.70 (bs, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.03 (dd, J = 7.0, 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.60-6.72 (m, 3H), 5.87 (s, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.54 (d, J = 6.2 Hz, 2H), 4.43 (bs, 2H), 3.78 (s, 6H), 3.68 (s, 3H).                             | 24,<br>33    |
| 292 | 433 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-(3,4,5-trimethoxyphenylamino)-pyrimidin-2-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 9.43 (s, 1H), 7.97 (m, 3H), 7.46 (bs, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (m, 3H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.08 (s, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.69 (bs, 2H), 3.65 (s, 9H).  | 24,<br>33    |
| 293 | 434 |    | CH | CH | N-(2-Amino-phenyl)-4-(3,4-dimethoxybenzylamino)-benzamide  | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.04 (s, 1H), 6.92-7.01 (m, 3H), 6.80-6.87 (m, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.62 (m, 1H), 4.87 (s, 2H, NH <sub>2</sub> ), 4.32 (d, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H).  | 33           |
| 294 | 435 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-pyrimidin-2-ylamino)-methyl]-benzamide                         | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.31 (bs, 1H), 7.21 (d, J = 7.5, 1H), 7.02 (dd, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.0, 7.0 Hz, 1H), 6.09 (d, J = 6.2 Hz, 1H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.54 (d, J = 5.7 Hz, 2H), 3.67 (s, 4H), 3.53 (s, 4H). | 24, 1,<br>33 |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization  | Schm      |
|-----|-----|---|----|----|---|---|-----------|
| 295 | 436 |    | CH | CH | N-(2-Amino-phenyl)-4-[[2-(1H-indol-3-yl)-ethylamino]-methyl]-benzamide                          | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 10.82 (s, 1H), 9.65 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.18-7.23 (m, 2H), 7.11 (dd, J = 7.0, 8.0 Hz, 1H), 7.01 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.51 (dd, J = 7.5, 6.6 Hz, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 3.89 (s, 2H), 2.89 (m, 4H). | 57        |
| 296 | 437 |    | CH | CH | N-(2-Amino-phenyl)-4-[[4-methylsulfanyl-phenylamino]-methyl]-benzamide                          | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.67 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.03 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.53 (m, 4H), 4.95 (s, 2H, NH <sub>2</sub> ), 4.41 (d, J = 5.7 Hz, 2H), 2.37 (s, 3H).   | 33        |
| 297 | 438 |    | CH | CH | N-(2-Amino-phenyl)-4-[[3-methylsulfanyl-phenylamino]-methyl]-benzamide                          | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.39-6.51 (m, 4H), 4.94 (s, 2H, NH <sub>2</sub> ), 4.41 (d, J = 5.7 Hz, 2H), 2.42 (s, 3H).  | 33        |
| 298 | 439 |   | CH | CH | N-(2-Amino-phenyl)-4-[[4-chloro-6-(3,4-dimethoxy-phenyl)-pyrimidin-2-ylamino]-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 8.37 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.68-7.79 (m, 2H), 7.55 (bs, 2H), 7.37 (s, 1H), 7.20 (d, J = 7.1 Hz, 1H), 7.11 (bs, 1H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.5, 7.5 Hz, 1H), 4.93 (s, 2H, NH <sub>2</sub> ), 4.86 (s, 2H), 3.88 (s, 6H).                        | 15, 33    |
| 299 | 440 |  | CH | CH | N-(2-Amino-phenyl)-4-[[4-(3,4-dimethoxy-phenyl)-pyrimidin-2-ylamino]-methyl]-benzamide          | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.64 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.89 (m, 1H), 7.72 (m, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.2 (d, J = 5.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.01 (m, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1H), 4.92 (s, 2H, NH <sub>2</sub> ), 4.68 (d, J = 6.2 Hz, 2H), 3.82 (s, 6H).        | 15, 1, 33 |

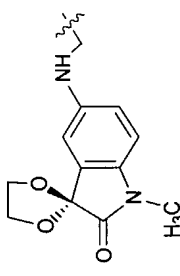
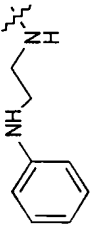
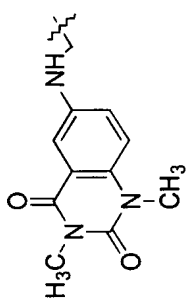
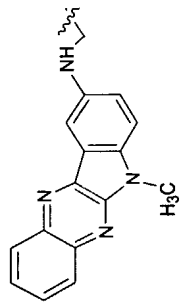


| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization  | Schm   |
|-----|-----|---|----|----|--|---|--------|
| 300 | 441 |    | CH | CH | 4-[(2-Acetyl-4,5-dimethoxyphenylamino)methyl]-N-(2-amino-phenyl)-benzamide                                       | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.68 (s, 1H), 9.45 (t, J = 5.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 6.6, 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.31 (s, 1H), 4.95 (s, 2H, NH <sub>2</sub> ), 4.63 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H).   | 33     |
| 301 | 442 |    | CH | CH | N-(2-Amino-phenyl)-4-[[4-(3,4-dimethoxyphenylamino)pyrimidin-2-ylamino]methyl]-benzamide                         | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD+CDCl <sub>3</sub> ) δ (ppm): 7.99 (d, J = 7.9 Hz, 2H), 7.80 (d, J = 6.2 Hz, 1H), 7.76 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.27 (m, 1H), 7.14 (m, 1H), 7.05 (dd, J = 2.2, 8.8 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.08 (d, J = 6.2 Hz, 1H), 4.75 (s, 2H), 3.79 (s, 3H), 3.42 (s, 3H).  | 1, 33  |
| 302 | 443 |   | CH | CH | N-(2-Amino-phenyl)-4-[[[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(3,4-dimethoxyphenyl)-aminol-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 6.6, 8.4 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.0 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.19 (dd, J = 2.6, 8.8 Hz, 1H), 4.93 (s, 2H), 4.67 (s, 2H), 3.88 (t, J = 5.7 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.60 (t, J = 5.5 Hz), 0.96 (s, 9H), 0.06 (s, 6H). | 33     |
| 303 | 444 |  | CH | CH | N-(2-Amino-phenyl)-4-[[[3,4-dimethoxyphenyl]-2-hydroxyethyl]-aminol-methyl]-benzamide                            | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.44 (s, 1H), 6.19 (d, J = 8.8 Hz, 1H), 4.94 (s, 2H), 4.79 (m, 1H), 4.66 (s, 2H), 3.67 and 3.71 (2s and broadening underneath, 8H), 3.55 (m, 2H).   | 33, 23 |

| Ex. | Cpd | W | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 304 | 445 |   | CH | N  | N-(2-Amino-phenyl)-6-[(3,4,5-trimethoxy-phenylamino)-methyl]-nicotinamide             | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.82 (s, 1H), 9.13 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (dd, J = 7.4, 7.7 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 7.4, 7.7 Hz, 1H), 6.31 (t, J = 5.8 Hz, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.48 (d, J = 5.8 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H).                | 33   |
| 305 | 446 |   | CH | N  | N-(2-Amino-phenyl)-6-[(2-oxo-4H-quinazolin-3-yl)-ethylamino]-nicotinamide             | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 8.69 (d, J = 2.2 Hz, 1H), 8.46 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.32-8.36 (m, 1H), 7.91-7.96 (m, 1H), 7.77 (m, 1H), 7.67 (m, 1H), 7.5 (m, 4H), 7.2 (s, 1H), 4.46 (t, J = 5.9 Hz, 1H), 4.09 (t, J = 5.9 Hz, 2H).  | 3    |
| 306 | 447 |   | CH | CH | N-(2-Amino-phenyl)-4-bis-(3-trifluoromethoxy-benzyl)-amino]-benzamide                 | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.37 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.54 (dd, J = 7.9, 7.9 Hz, 2H), 7.18-7.37 (m, 6H), 7.17 (d, J = 7.0 Hz, 1H), 6.99 (dd, J = 7.0, 7.9 Hz, 1H), 6.82 (m, 3H), 6.63 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (s, 4H), 4.86 (s, 2H).   | 33   |
| 307 | 448 |   | CH | CH | N-(2-Amino-phenyl)-4-[(2-dimethylamino-benzothiazol-5-ylamino)-methyl]-benzamide      | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.58 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.44 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 5.7 Hz, 1H), 4.88 (bs, 2H), 4.37 (d, J = 5.7 Hz, 2H), 3.06 (s, 6H).   | 33   |
| 308 | 449 |   | CH | CH | N-(2-Amino-phenyl)-4-[(2-oxo-2,3-dihydro-1H-benzotriazin-5-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 10.2 (s, 1H), 10.1 (s, 1H), 9.62 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 8.4 Hz, 1H), 6.30 (s, 1H), 4.89 (bs, 2H), 4.72 (s, 2H). | 33   |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization   | Schm |
|-----|-----|---|----|----|---|--|------|
| 309 | 450 |    | CH | CH | N-(2-Amino-phenyl)-4-[(4-trifluoromethylsulfonyl-phenylamino)-methyl]-benzamide                   | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.60 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 6.2 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 7.9 Hz, 1H), 4.88 (bs, 2H), 4.72 (d, J = 6.2 Hz, 2H).   | 33   |
| 310 | 451 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2-pyridin-3-ylmethylsulfonyl)-1H-benzimidazol-5-ylamino]-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD) δ (ppm): 8.67 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 1.3, 4.4 Hz, 1H), 8.08 (s, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.36-7.30 (m, 3H), 7.20-7.15 (m, 1H), 7.08 (dt, J = 1.3, 8.4 Hz, 1H), 6.94 (dd, J = 1.3, 7.9 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H), 4.20 (bs, 2H), 3.36 (s, 2H). | 33   |
| 311 | 452 |    | CH | CH | N-(2-Amino-phenyl)-4-[(2-pyridin-3-ylmethylsulfonyl)-benzoxazol-5-ylamino]-methyl]-benzamide      | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD) δ (ppm): 8.60 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.87 (m, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 6.6 Hz, 1H), 7.20-7.15 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.66 (s, 1H), 6.61 (d, J = 8.8 Hz, 1H), 4.87 (s, 2H), 4.45 (s, 2H), 4.37 (s, 2H), 3.35 (s, 2H).   | 33   |
| 312 | 453 |  |    |    | N-(2-Amino-5-trifluoromethyl-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide             | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.21 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.54 (m, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.41-7.34 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 2.2 Hz, 1H), 6.20 (dd, J = 2.2, 8.8 Hz, 1H), 4.43 (s, 2H), 4.29 (s, 2H), 3.84 (s, 6H).   | 33   |

| Ex. | Cpd | W | Y  | Z  | Name   | Characterization  | Schm |
|-----|-----|---|----|----|--|---|------|
| 313 | 454 |   |    |    | N-(2-Amino-4,5-difluoro-phenyl)-4-[[3,4-dimethoxy-phenylamino]-methyl]-benzamide                         | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.21 (s, 1H); 7.84 (d, J = 7.9 Hz, 2H); 7.45 (d, J = 7.9 Hz, 2H); 7.20 (dd, J = 2.6, 8.4 Hz, 1H); 6.76 (d, J = 8.8 Hz, 1H); 6.57 (dd, J = 3.9, 7.9 Hz, 1H); 6.32 (d, J = 2.6 Hz, 1H); 6.16 (dd, J = 2.6, 8.4 Hz, 1H); 4.40 (s, 2H); 3.82 (s, 9H).   | 33   |
| 314 | 455 |   | CH | CH | N-(2-Amino-phenyl)-4-[[2-oxo-2,3-dihydro-benzooxazol-5-ylamino]-methyl]-benzamide                        | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.60 (s, 1H); 7.93 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.16 (d, J = 7.5 Hz, 1H); 6.97 (m, 2H); 6.78 (d, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.35 (t, J = 5.7 Hz, 1H); 6.27 (m, 2H); 4.88 (bs, 2H); 4.34 (d, J = 6.2 Hz, 2H).  | 33   |
| 315 | 456 |   | CH | CH | N-(2-Amino-phenyl)-4-[[2-methylamino-benzothiazol-5-ylamino]-methyl]-benzamide                           | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 7.92 (d, J = 7.9 Hz, 2H); 7.66 (d, J = 4.4 Hz, 1H); 7.49 (d, J = 7.9 Hz, 2H); 7.26 (d, J = 8.4 Hz, 1H); 7.15 (d, J = 7.9 Hz, 1H); 6.96 (d, J = 8.4 Hz, 1H); 6.59 (t, J = 7.9 Hz, 1H); 6.53 (s, 1H); 6.40 (dd, J = 1.3, 8.4 Hz, 1H); 6.28 (t, J = 5.7 Hz, 1H); 4.88 (bs, 2H); 4.36 (d, J = 5.7 Hz, 2H); 2.85 (d, J = 4.4 Hz, 3H).  | 33   |
| 316 | 457 |   |    |    | N-(2,6-Diamino-phenyl)-4-[[3,4-dimethoxy-phenylamino]-methyl]-benzamide                                  | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) δ (ppm): 8.09 (s, 1H); 7.88 (d, J = 7.5 Hz, 2H); 7.48 (d, J = 7.5 Hz, 2H); 6.97 (d, J = 7.9 Hz, 1H); 6.73 (d, J = 8.4 Hz, 2H); 6.64 (d, J = 7.9 Hz, 1H); 6.29 (s, 1H); 6.14 (d, J = 8.4 Hz, 1H); 4.39 (s, 2H); 3.81 (s, 3H); 3.80 (s, 3H); 3.70 (bs, 5H).  | 33   |
| 317 | 458 |   | CH | CH | N-(2-Amino-phenyl)-4-[[2-(2-methoxyethyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-ylamino]-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.61 (s, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.73 (t, J = 5.7 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.47 (d, J = 7.9 Hz, 2H); 7.15 (d, J = 7.9 Hz, 1H); 6.97 (d, J = 7.5 Hz, 1H); 6.92 (bs, 1H); 6.86 (d, J = 8.4 Hz, 1H); 6.77 (d, J = 7.9 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 4.89 (bs, 2H); 4.54 (d, J = 5.7 Hz, 2H); 3.65 (t, J = 5.3 Hz, 2H); 3.47 (t, J = 5.3 Hz, 2H); 3.20 (s, 3H). | 33   |

| Ex. | Cpd | W   | Y  | Z  | Name  | Characterization  | Schm |
|-----|-----|---|----|----|---|---|------|
| 318 | 459 |    | CH | CH | N-(2-Amino-phenyl)-4-[(3-spiro[1',2']dioxolane-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-ylamino)-methyl]-benzamide | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 8.3 Hz, 2H); 7.46 (d, J = 8.3 Hz, 2H); 7.15 (d, J = 7.5 Hz, 1H); 6.96 (t, J = 7.0 Hz, 1H); 6.78-6.71 (m, 3H); 6.62-6.54 (m, 2H); 6.26 (t, J = 7.5 Hz, 1H); 4.87 (s, 2H); 4.36-4.32 (m, 4H); 4.23-4.19 (m, 2H); 2.98 (s, 3H).   | 33   |
| 319 | 460 |    | CH | N  | N-(2-Amino-phenyl)-6-(2-phenylamino-ethylamino)-nicotinamide  | <sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD) δ (ppm): 8.67 (d, J = 2.2 Hz, 1H); 7.97 (dd, J = 2.5, 8.9 Hz, 1H); 7.58 (m, 1H); 7.51 (m, 1H); 7.15 (dd, J = 1.1, 7.7 Hz, 1H); 7.08 (m, 2H); 6.89 (dd, J = 1.4, 8.0 Hz, 1H); 6.76 (dt, J = 4.4, 7.7 Hz, 1H); 6.67 (d, J = 7.7 Hz, 2H); 6.60 (m, 2H); 4.87 (bs, 2H); 3.60 (t, J = 6.3 Hz, 2H); 3.35 (t, J = 6.3 Hz, 2H).  | 33   |
| 320 | 461 |    | CH | CH | N-(2-Amino-phenyl)-4-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-ylamino)-methyl]-benzamide         | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.22 (d, J = 8.8 Hz, 1H); 7.16-7.09 (m, 3H); 6.96 (t, J = 7.5 Hz, 1H); 6.76 (d, J = 7.9 Hz, 1H); 6.65-6.56 (m, 2H); 4.87 (s, 2H); 4.42 (d, J = 5.3 Hz, 2H); 3.44 (s, 3H); 3.26 (s, 3H).   | 33   |
| 321 | 462 |  | CH | CH | N-(2-Amino-phenyl)-4-[(6-methyl-6H-indolo[2,3-b]quinoxalin-9-ylamino)-methyl]-benzamide                         | <sup>1</sup> H NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.60 (s, 1H); 8.19 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.76 (t, J = 7.0 Hz, 1H); 7.65 (t, J = 7.9 Hz, 1H); 7.57 (d, J = 7.9 Hz, 2H); 7.54 (d, J = 8.8 Hz, 1H); 7.41 (d, J = 1.3 Hz, 1H); 7.22 (dd, J = 1.8, 8.8 Hz, 1H); 7.14 (d, J = 7.9 Hz, 1H); 6.95 (t, J = 7.5 Hz, 1H); 6.76 (t, J = 7.9 Hz, 1H); 6.57 (t, J = 7.5 Hz, 1H); 6.51 (bs, 1H); 4.86 (bs, 2H); 4.54 (d, J = 4.8 Hz, 2H); 3.85 (s, 3H). | 33   |

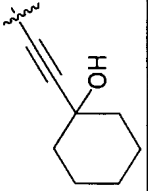
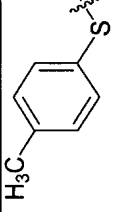
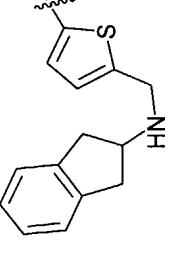
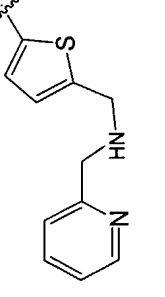
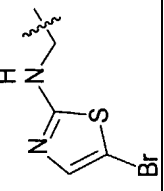
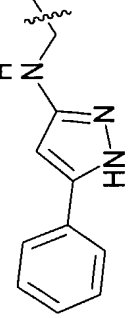
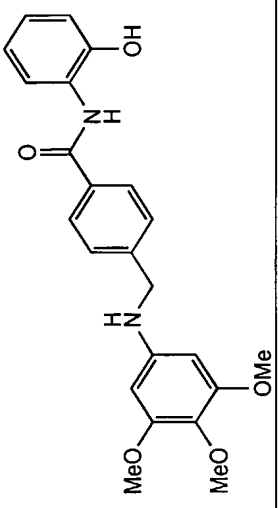
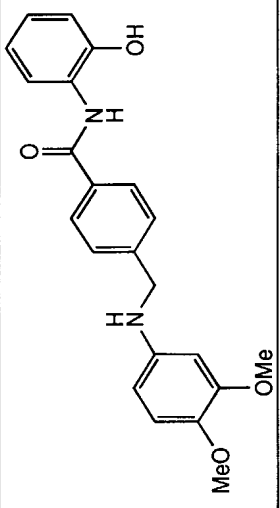
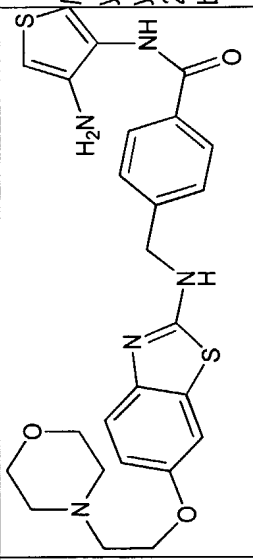
| Ex. | Cpd | W   | Y  | Z  | Name   | Characterization                                  | Schm  |
|-----|-----|---|----|----|--|---|-------|
| 322 | 463 |    | N  | CH | N-(2-Amino-phenyl)-6-(1-hydroxy-cyclohexylethynyl)-nicotinamide                  | LRMS calc: 335.40, found: 336.1 (MH) <sup>+</sup> | 14, 3 |
| 323 | 464 |    | N  | CH | N-(2-Amino-phenyl)-6-p-tolylsulfanyl-nicotinamide                                | LRMS calc: 335.42, found: 336.1 (MH) <sup>+</sup> | 14, 3 |
| 324 | 465 |    | CH | CH | N-(2-Amino-phenyl)-4-[5-(indan-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide   | LRMS calc: 453.6, found: 454.2 (MH) <sup>+</sup>  | 21    |
| 325 | 466 |    | CH | CH | N-(2-Amino-phenyl)-4-[5-(pyridin-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide | LRMS calc: 414.52, found: 415 (MH) <sup>+</sup>   | 21    |
| 326 | 467 |   | CH | CH | N-(2-Amino-phenyl)-4-[(5-bromo-thiazol-2-ylamino)-methyl]-benzamide              | LRMS calc: 403.3, found: 404 (MH) <sup>+</sup>    | 21    |
| 327 | 468 |  | CH | CH | N-(2-Amino-phenyl)-4-[(5-phenyl-1H-pyrazol-3-ylamino)-methyl]-benzamide          | LRMS calc: 483.45, found: 484.1 (MH) <sup>+</sup> | 21    |

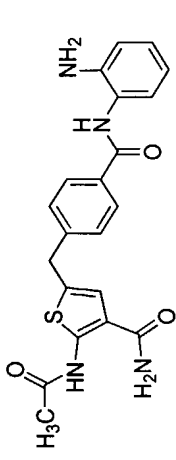
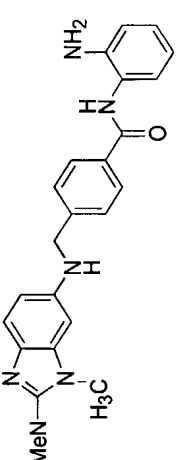
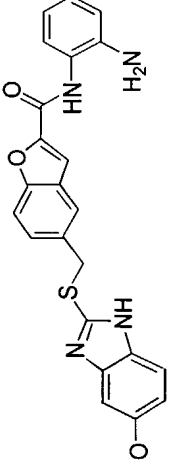
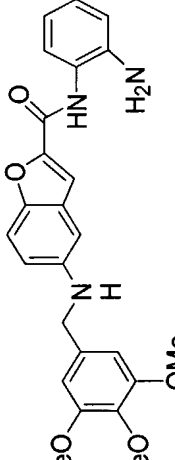
Table 4c

## Characterization of Additional Compounds

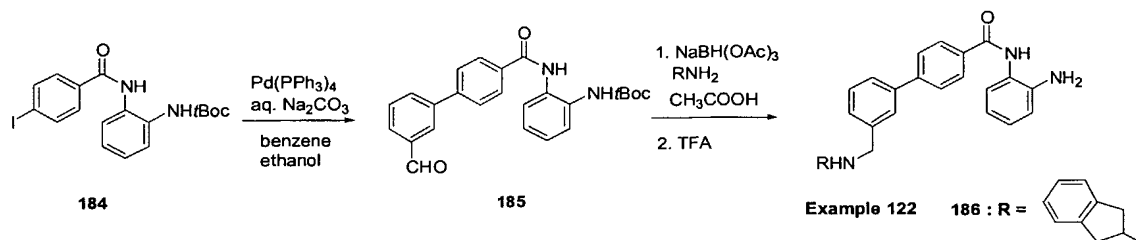
| Ex. | Cpd | Compound   | Name  | Characterization   | Schm   |
|-----|-----|--|---|--|--------|
| 426 | 571 |   | N-(2-Hydroxy-phenyl)-4-<br>[(3,4,5-trimethoxy-<br>phenylamino)-methyl]-<br>benzamide                              | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 9.57 (brs, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.07 (t, J = 8.3 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.9 Hz, 1H), 6.21 (t, J = 6.1 Hz, 1H), 5.95 (s, 2H), 4.38 (d, J = 5.7 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H).   | 33, 55 |
| 427 | 572 |   | N-(2-hydroxy-phenyl)-4-<br>[(3,4-Dimethoxy-<br>phenylamino)-methyl]-<br>benzamide                                 | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.9 (bs, 1H), 9.53 (s, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.08 (dd, J = 7.5, 7.5 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.88 (dd, J = 7.5, 7.5 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.38 (s, 1H), 6.05 (m, 2H), 4.36 (d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).                      | 33, 55 |
| 428 | 573 |  | N-(4-Amino-thiophen-3-<br>yl)-4-[[6-(2-morpholin-4-<br>ylethoxy)-benzothiazol-<br>2-ylamino]methyl]-<br>benzamide | <sup>1</sup> H NMR: (Acetone-d <sub>6</sub> ) δ (ppm): 9.09 (bs, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.96 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 3.5 Hz, 1H), 7.51 (bs, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 6.95 (d, J = 6.2 Hz, 1H), 6.35 (d, J = 3.5 Hz, 1H), 4.85 (s, 2H), 4.20 (t, J = 5.7 Hz, 2H), 3.69 (t, J = 4.4 Hz, 4H), 2.87-2.81 (m, 2H), 2.62-2.57 (m, 4H). | 33, 60 |

| Ex. | Cpd | Compound | Name  | Characterization  | Schm   |
|-----|-----|----------|---|---|--------|
| 429 | 574 |          | N-(4-Amino-thiophen-3-yl)-4-[(3,4,5-trimethoxyphenylamino)methyl]-benzamide           | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 9.66 (brs, 1H), 7.94 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 6.22-6.16 (m, 1H), 5.94 (s, 2H), 4.91 (s, 2H), 4.38 (d, J = 5.7 Hz, 4H), 3.70 (s, 6H), 3.55 (s, 3H).   | 33, 60 |
| 430 | 575 |          | N-(4-Amino-thiophen-3-yl)-4-(5-methoxy-1H-benzimidazol-2-yl)sulfanylmethyl)-benzamide | (DMSO) δ (ppm): 12.43 (bs, 1H), 9.59 (bs, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.32 (bs, 1H, SCH), 6.96 (bs, 1H, SCH), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 6.11 (d, J = 3.7 Hz, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 3.76 (s, 3H). LRMS: 410.1 (calc) (M); 411.2 (found) (M+H)+   | 36, 60 |
| 431 | 576 |          | 2-(4-(4-Methoxybenzylamino)phenyl)-cyclopropanecarboxylic acid (2-amino-phenyl)-amide | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.63 (d, J = 7.1 Hz, 1H), 7.53 (t, J = 4.2 Hz, 1H), 7.41 (dd, J = 9.2, 1.5 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 6.62-6.59 (m, 3H), 4.51 (d, J = 4.2 Hz, 2H), 3.78 (s, 3H), 2.77 (d, J = 3.1 Hz, 1H), 2.45 (d, J = 1.1 Hz, 1H), 1.22 (m, 1H), 1.05 (m, 1H). |        |
| 432 | 577 |          | N-(2-Amino-phenyl)-4-(3-cyano-6-methylpyridin-2-yl)oxybenzyl)-benzamide               | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.72 (brs, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 5.62 (brs, 2H), 4.97 (brs, 2H)   | 11     |
| 433 | 578 |          | N-(2-Amino-phenyl)-4-((6-methoxy-pyridin-3-yl)pyrimidin-2-ylamino)methyl)-benzamide   | <sup>1</sup> H NMR (300 MHz, DMSO-D <sub>6</sub> ) δ (ppm): 9.63 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 5.3 Hz, 2H), 7.96 (m, 3H), 7.54 (d, J = 7.5 Hz, 2H), 7.22 (dd, J = 5.3, 7.8 Hz, 2H), 7.01 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.64 (dd, J = 7.0, 7.9 Hz, 1H), 4.92 (s, 2H), 4.70 (d, J = 6.2 Hz, 2H), 3.98 (s, 3H).   | 15, 33 |



| Ex. | Cpd | Compound   | Name  | Characterization  | Schm |
|-----|-----|--|---|---|------|
| 434 | 579 |   | 2-Acetylamino-5-{4-(2-amino-phenylcarbamoyl)-benzyl}thiophene-3-carboxamide                         | <sup>1</sup> H NMR: (DMSO) δ (ppm): 11.98 (bs, 1H), 9.61 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.81 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.88 (bs, 2H), 4.10 (s, 2H), 2.15 (s, 3H).                             | 49   |
| 435 | 580 |   | N{2-Amino-phenyl}-4-[(3-methyl-2-methylamino-3H-benzimidazol-5-ylamino)methyl]benzamide             | <sup>1</sup> H NMR (DMSO) δ (ppm): 9.56 (s, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 13.2, 8.35 Hz, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.39 (s, 1H), 6.31 (m, 2H), 5.75 (t, J = 6.15 Hz, 1H), 4.87 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.82 (d, J = 8.5 Hz, 3H). | 61   |
| 438 | 591 |   | 5-(5-Methoxy-1H-benzimidazol-2-yl)sulfanylmethyl)benzofuran-2-carboxylic acid (2-amino-phenyl)amide | <sup>1</sup> H NMR (DMSO) δ (ppm): 9.84 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.78-6.74 (m, 3H), 6.59 (t, J = 7.5 Hz, 1H), 5.71 (s, 2H), 4.94 (s, 1H), 4.65 (s, 2H), 3.76 (s, 3H).   | 64   |
| 439 | 592 |  | 5-(3,4,5-Trimethoxybenzylamino)benzofuran-2-carboxylic acid (2-amino-phenyl)amide                   | <sup>1</sup> H NMR (DMSO) δ (ppm): 9.69 (s, 1H), 7.47 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 6.6 Hz, 1H), 6.97 (dd, J = 7.5, 7.5 Hz, 1H), 6.89 (dd, J = 8.8, 2.2 Hz, 1H), 6.79-6.78 (m, 2H), 6.74 (s, 2H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 6.14 (t, J = 5.7 Hz, 1H), 4.92 (s, 2H), 4.21 (d, J = 5.7 Hz, 1H), 3.75 (s, 6H), 3.31 (s, 3H).           | 64   |

## Scheme 21



## Example 122

Step 1: {2-[(3'-Formyl-biphenyl-4-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (**185**)

**[0250]** Following the procedure described in Example 15, step 1, but substituting 184 for 140, the title compound 185 was obtained in 74% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.10 (s, 1H), 9.41 (s, 1H), 8.13 (m, 1H), 8.07 (d,  $J = 8.4$  Hz, 2H), 7.89 (m, 2H), 7.77 (m, 1H), 7.70 (d,  $J = 8.4$  Hz, 2H), 7.64 (m, 1H), 7.27-7.09 (m, 3H), 7.03 (s, 1H), 1.52 (s, 9H).

Step 2: *N*-(2-Aminophenyl)-4-[3-(indan-2-ylaminomethyl)phenyl]-benzamide (**186**)

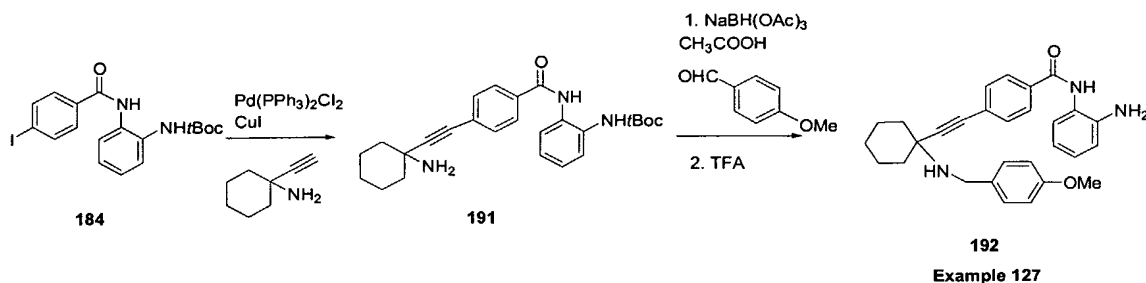
**[0251]** To a stirred solution of biphenyl aldehyde (104 mg, 0.25 mmol) and 2-aminoindane (33.3 mg, 0.25 mmol) in dichloroethane (1 mL) was added sodium triacetoxyborohydride (80 mg, 0.375 mmol) followed by a glacial acetic acid (15  $\mu\text{L}$ , 0.25 mmol), and then the mixture was stirred at room temperature for 3h. After a removal of the volatiles, the residue was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The combined organic layers were washed with water, dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired Boc-monoprotected product (112 mg, 84% yield) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.21 (s, 1H), 8.03 (d,  $J = 8.7$  Hz, 2H), 7.83 (m, 1H), 7.69 (d,  $J = 8.7$  Hz, 2H), 7.65 (s, 1H), 7.54-7.38 (m, 3H), 7.28 (m, 7H), 6.82 (s, 1H), 3.95 (s, 2H), 3.74 (m, 1H), 3.22 (dd,  $J = 15.6, 6.9$  Hz, 2H), 2.89 (dd,  $J = 15.6, 6.6$  Hz, 2H), 1.53 (s, 9H).

**[0252]** Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **186** was obtained in 98 % yield.  $^1\text{H}$  NMR (20%  $\text{CD}_3\text{OD}$  in  $\text{CDCl}_3$ ):  $\delta$  7.95 (d,  $J = 8.4$  Hz, 2H), 7.65 (d,  $J = 8.4$  Hz, 2H), 7.57 (m, 1H), 7.54-6.79 (m, 11H), 3.95 (s, 2H), 3.66 (m, 1H), 3.16 (dd,  $J = 15.6, 6.9$  Hz, 2H), 2.81 (dd,  $J = 15.6, 6.6$  Hz, 2H).

## Examples 123-126

**[0253]** Examples 123 to 126 (compounds 187 - 190) were prepared using the same procedure as described for compound 186 in Example 122 (scheme 21).

## Scheme 22



## Example 127

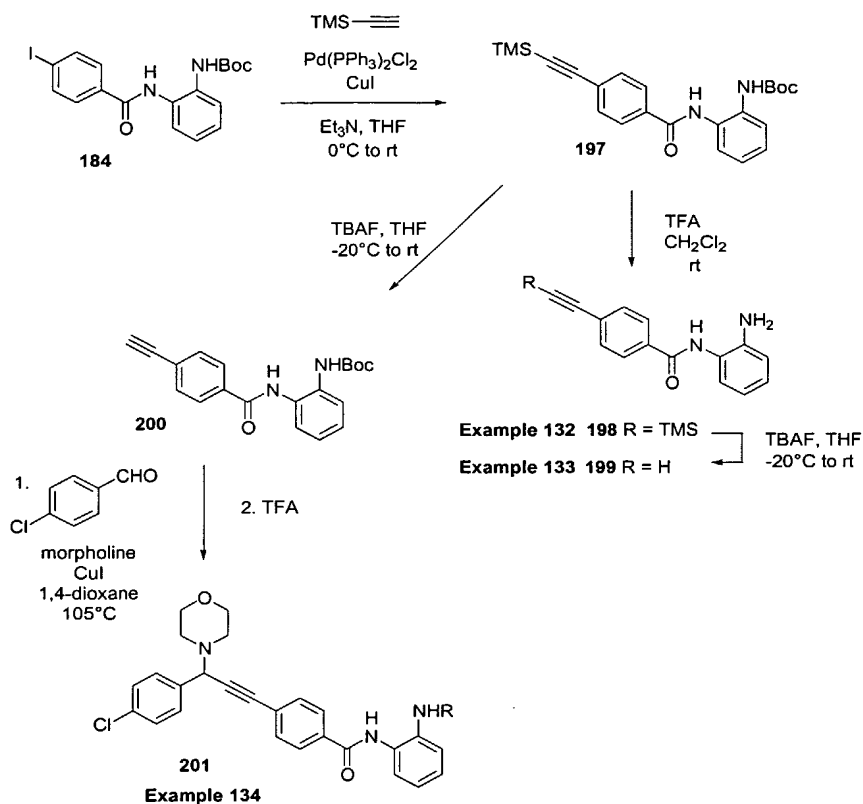
Step 1: {2-[4-(1-Amino-cyclohexylethynyl)-benzoylamino]-phenyl}-carbamic acid *tert*-butyl ester (**191**)

**[0254]** A mixture of iodide **184** (438 mg, 1.0 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (35 mg, 0.05 mmol), triphenylphosphine (7.6 mg, 0.025 mmol), and 1-ethynylcyclohexylamine (185 mg, 1.5 mmol) was stirred at room temperature in THF (4 mL) containing triethylamine (0.56 mL, 4.0 mmol) for 20 min. To this CuI (3.8 mg, 0.02 mmol) was added and stirring continued for 2 h. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with water, and the organic layer was dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired product **191** (420 mg, 97% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.36 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.25-6.85 (m, 3H), 2.10-1.30 (m, 10H), 1.51 (s, 9H).

Step 2: *N*-(2-Aminophenyl)-4-[1-(4-methoxy-benzylamino)-cyclohexylethynyl]-benzamide (**192**)

**[0255]** Following the procedure described in Example 122, step 2, but substituting *p*-anisaldehyde for 2-aminoindane, the title compound **192** was obtained in 74 % yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.44 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.23 (m, 1H), 7.05 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.78 (m, 2H), 3.97 (s, 2H), 3.76 (s, 3H), 2.10-1.30 (m, 10H).

**Scheme 23**



**Example 133**

Step 1: N-[2-(*t*-Butyloxycarbonyl)-amino-phenyl]-4-(trimethylsilylethynyl)benzamide (**197**)

**[0256]** To a stirred solution of **184** (5.00 g, 11.41 mmol) in anhydrous THF (100 ml) under nitrogen at 0°C were added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (240 mg, 0.34 mmol), CuI (130 mg, 0.69 mmol), and trimethylsilylacetylene (2.10 ml, 14.84 mmol), respectively. Then, anhydrous Et<sub>3</sub>N (6.36 ml, 45.66 mmol) was added dropwise. The temperature was slowly warmed up to room temperature over 4 h. The reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 20/80→50/50) to afford the title compound **197** (4.42 g, 10.83 mmol, 94% yield) as a yellow powder. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.26 (bs, 1H), AB system (δ<sub>A</sub> = 7.91, δ<sub>B</sub> = 7.55, J = 8.3 Hz, 4H), 7.85 (d, J = 7.9 Hz, 1H), 7.32-7.13 (m, 3H), 6.70 (bs, 1H), 1.53 (s, 9H), 0.28 (s, 9H).

Step 2: *N*-(2-Amino-phenyl)-4-(trimethylsilylethynyl)benzamide (**198**)

**[0257]** Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **198** (70 mg, 0.23 mmol) was obtained as a white solid with a major fraction composed of a mixture of **198** and **199**. <sup>1</sup>H NMR (300 MHz, acetone-d<sub>6</sub>) δ (ppm): 9.20 (bs, 1H), AB system (δ<sub>A</sub> = 8.07, δ<sub>B</sub> = 7.62, J = 8.2 Hz, 4H), 7.32 (d, J = 7.6 Hz, 1H), 7.05 (td, J = 7.6, 1.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 4.66 (bs, 2H), 0.30 (s, 9H).

Step 3: *N*-(2-Amino-phenyl)-4-ethynylbenzamide (**199**)

**[0258]** To a stirred solution at -20°C of a mixture of **198** and **199** in anhydrous THF (15 ml) under nitrogen was added a solution of TBAF (1 ml, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 18 h. Then, the reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 30/70) to afford the title compound **199** (215 mg, 0.91 mmol, 46% yield over 2 steps) as a pale yellow powder. <sup>1</sup>H NMR (300 MHz, acetone-d<sub>6</sub>) δ (ppm): 9.19 (bs, 1H), AB system (δ<sub>A</sub> = 8.08, δ<sub>B</sub> = 7.66, J = 8.5 Hz, 4H), 7.33 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 4.67 (bs, 2H), 3.88 (s, 1H).

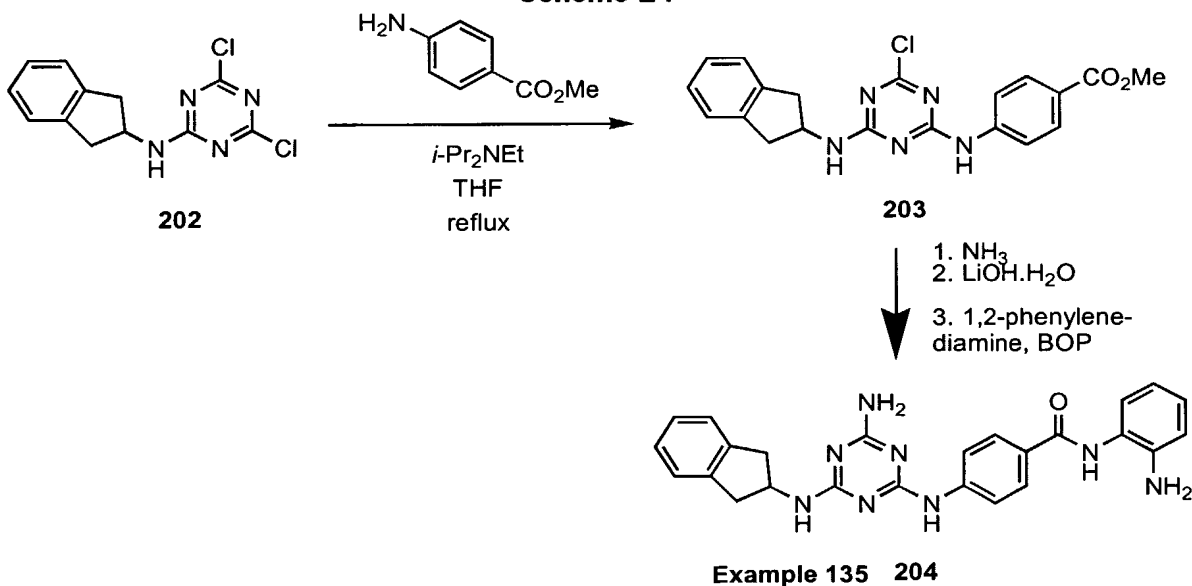
**Example 134**Step 1: *N*-[2-(*t*-Butyloxycarbonyl)-amino-phenyl]-4-ethynylbenzamide (**200**)

**[0259]** To a stirred solution at -20°C of a mixture of **199** (3.48 g, 8.53 mmol) in anhydrous THF (50 ml) under nitrogen was slowly added a solution of TBAF (9.4 ml, 9.38 mmol, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 4 h. Then, the reaction mixture was concentrated, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 25/75→30/70) to afford the title compound **200** (2.53 g, 7.53 mmol, 88% yield) as a pale yellow foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.31 (bs, 1H), AB system (δ<sub>A</sub> = 7.94, δ<sub>B</sub> = 7.59, J = 8.5 Hz, 4H), 7.83 (d, J = 7.6 Hz, 1H), 7.30-7.10 (m, 3H), 6.75 (bs, 1H), 3.23 (s, 1H), 1.53 (s, 9H).

**Step 2: *N*-(2-amino-phenyl)-4-[3-(4-chlorophenyl)-3-morpholin-4-yl-1-propyn-1-yl]-benzamide (**201**)**

To a stirred solution at room temperature of **200** (200 mg, 0.60 mmol) in anhydrous 1,4-dioxane (5 ml) under nitrogen were added 4-chlorobenzaldehyde (100 mg, 0.71 mmol), morpholine (60  $\mu$ l, 0.68 mmol), and CuI (6 mg, 0.03 mmol), respectively. The reaction mixture was bubbled with nitrogen for 5 min and warmed up to 105°C. After 18 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the desired compound (193 mg, 0.35 mmol, 59% yield) as a pale yellow foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 9.40 (bs, 1H), AB system ( $\delta_A = 7.96$ ,  $\delta_B = 7.36$ ,  $J = 8.5$  Hz, 4H), 7.79 (d,  $J = 7.9$  Hz, 1H), 7.59 (d,  $J = 8.4$  Hz, 4H), 7.25-7.10 (m, 3H), 6.91 (s, 1H), 4.80 (s, 1H), 3.82-3.68 (m, 4H), 2.69-2.58 (m, 4H), 1.53 (s, 9H).

**[0260]** Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **201** was obtained in 67 % yield. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 9.80 (bs, 1H), AB system ( $\delta_A = 8.06$ ,  $\delta_B = 7.71$ ,  $J = 8.1$  Hz, 4H), AB system ( $\delta_A = 7.65$ ,  $\delta_B = 7.52$ ,  $J = 8.3$  Hz, 4H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.02 (t,  $J = 7.3$  Hz, 1H), 6.82 (d,  $J = 7.0$  Hz, 1H), 6.64 (t,  $J = 7.5$  Hz, 1H), 5.10 (s, 1H), 4.97 (bs, 2H), 3.72-3.58 (m, 4H), 2.67-2.46 (m, 4H).

**Scheme 24**

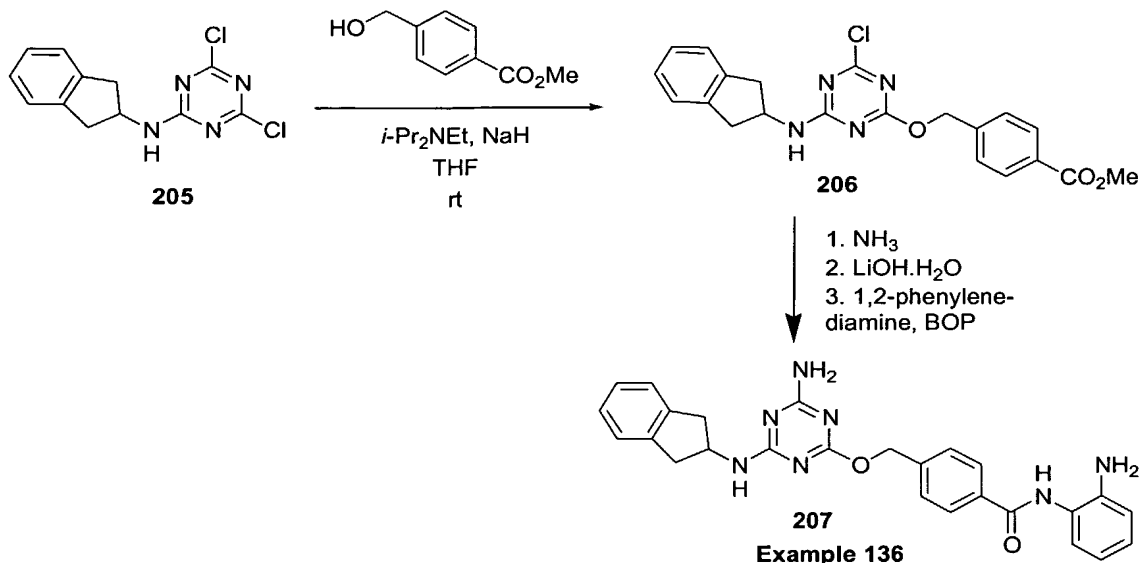
**Example 135****Step 1: Methyl 4-(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-benzoic ester (203)**

**[0261]** To a stirred solution at room temperature of **202** (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*Pr<sub>2</sub>NEt (1.86 ml, 10.66 mmol) and methyl 4-aminobenzoate (1.29 g, 8.53 mmol) or ArNH<sub>2</sub> (1.2 equiv), respectively. The reaction mixture was then refluxed for 24 h. After cooling, the reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH<sub>2</sub>Cl<sub>2</sub>: 2/98→5/95) to afford the title compound **203** (1.70 g, 4.30 mmol, 60% yield) as a beige powder. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): mixture of rotamers, 2 AB system (δ<sub>A</sub> = 8.03, δ<sub>A'</sub> = 8.00, δ<sub>B</sub> = 7.70, δ<sub>B'</sub> = 7.61, J<sub>AB</sub> = J<sub>A'B'</sub> = 8.8 Hz, 4H), 7.43 and 7.31 (2 bs, 1H), 7.29-7.19 (m, 4H), 5.84 and 5.78 (2 d, J = 7.2 and 7.7 Hz, 1H), 4.98-4.77 (2 m, 1H), 3.91 and 3.90 (2 s, 3H), 3.41 (dd, J = 16.1, 7.0 Hz, 2H), 2.94 and 2.89 (2 dd, J = 15.9, 4.9 Hz, 2H).

**Step 2: 4-[4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide (204)**

**[0262]** The title compound **204** was obtained from **203** in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. <sup>1</sup>H NMR (300 MHz, acetone-d<sub>6</sub>) δ (ppm): mixture of rotamers, 8.98 (m, 1H), 8.49 and 8.28 (2m, 1H), 8.10-7.92 (m, 4H), 7.35-7.14 (m, 5H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 6.6, 1.3 Hz, 1H), 6.71 (td, J = 7.6, 1.3 Hz, 1H), 6.57 and 6.42 (2m, 1H), 6.04 and 5.86 (2m, 2H), 4.92-4.76 (m, 1H), 4.70-4.58 (m, 1H), 3.44-3.26 (m, 2H), 3.08-2.92 (m, 2H). HRMS (calc.): 452.2073, (found): 452.2062.

## Scheme 25



## Example 136

Step 1: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yloxy)-methyl]-benzoic ester (**206**)

**[0263]** To a stirred solution at 0°C of **205** (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*-Pr<sub>2</sub>NEt (1.86 ml, 10.66 mmol) and methyl 4-(hydroxymethyl)benzoate (1.30 g, 7.82 mmol). After few minutes, NaH (95%, 186 mg, 7.11 mmol) was added portionwise. Then, the reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH<sub>2</sub>Cl<sub>2</sub>: 2/98) to afford the title compound **206** (2.00 g, 4.88 mmol, 69% yield) as a colorless sticky foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): mixture of rotamers, 2 AB system (δ<sub>A</sub> = 8.06, δ<sub>A'</sub> = 8.03, δ<sub>B</sub> = 7.52, δ<sub>B'</sub> = 7.46, J<sub>AB</sub> = J<sub>A'B'</sub> = 8.5 Hz, 4H), 7.26-7.17 (m, 4H), 5.94 and 5.85 (2 bd, J = 7.8 Hz, 1H), 5.48 and 5.39 (2 s, 2H), 4.92-4.76 (2 m, 1H), 3.94 and 3.92 (2 s, 3H), 3.39 and 3.33 (2 dd, J = 16.0, 7.0 Hz, 2H), 2.89 and 2.84 (2 dd, J = 16.0, 4.9 Hz, 2H).

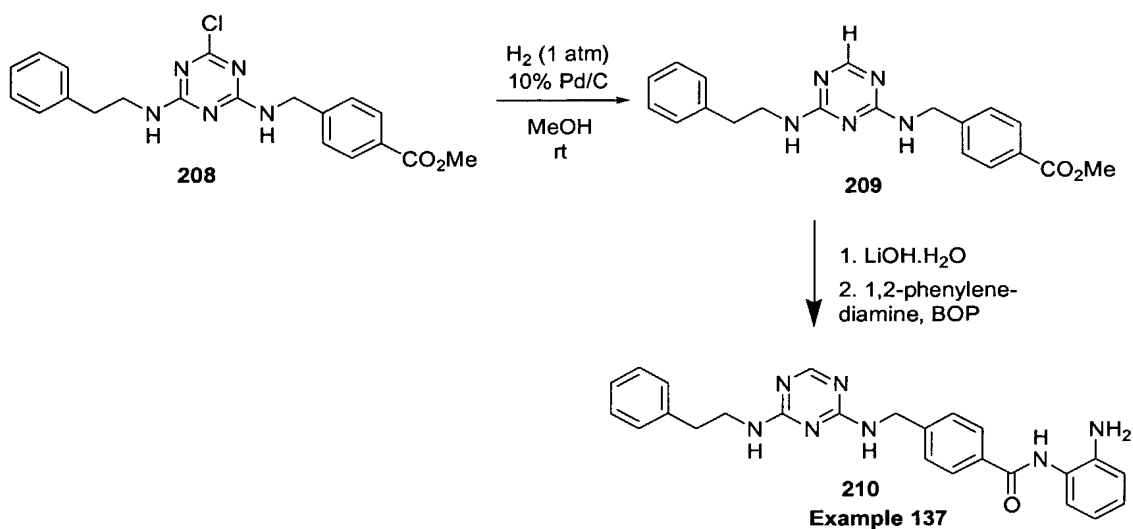
Step 2: 4-[(4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yloxy)-methyl]-N-(2-amino-phenyl)-benzamide (**207**)

**[0264]** The title compound **207** was obtained from **206** in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. <sup>1</sup>H NMR (300 MHz, acetone-d<sub>6</sub> + □ DMSO-d<sub>6</sub>) δ (ppm): 9.49 (m,



1H), 8.12-8.03 (m, 2H), 7.60 (t,  $J = 7.7$  Hz, 2H), 7.35 (d,  $J = 7.1$  Hz, 1H), 7.28-7.13 (m, 4H), 7.07-6.94 (m, 2H), 6.90 (dd,  $J = 7.3, 1.4$  Hz, 1H), 6.70 (td,  $J = 7.3, 1.1$  Hz, 1H), 6.44 (bs, 1H), 6.25 (bs, 1H), 5.47 and 5.41 (2s, 2H), 4.87-4.68 (m, 3H), 3.35-3.20 (m, 2H), 3.02-2.88 (m, 2H). HRMS (calc.): 467.2070, (found): 467.2063.

### Scheme 26



### Example 210

#### Methyl 4-[(4-chloro-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (208)

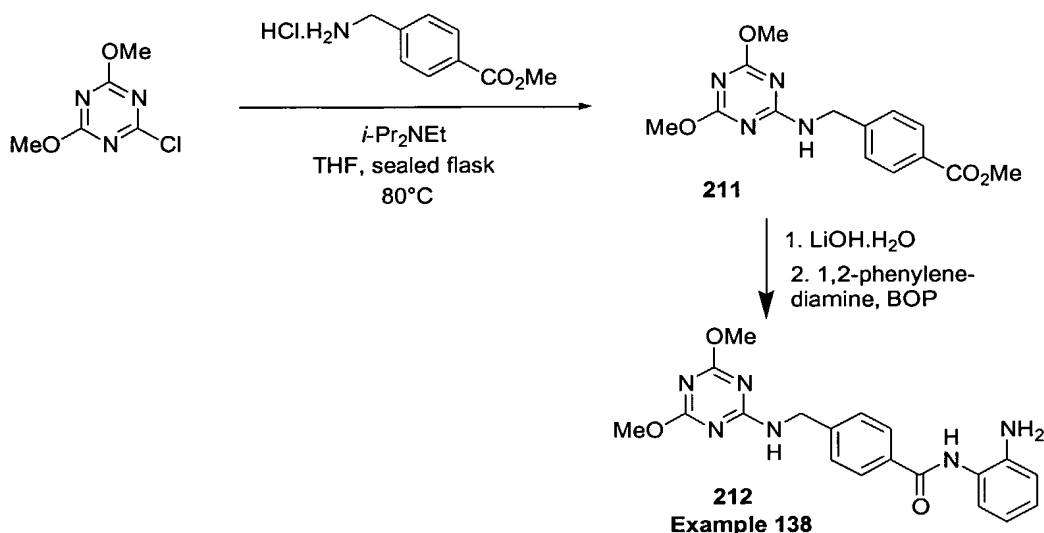
**[0265]** The title compound **208** was obtained from **2** following the same procedure as in Example 1, pathway B steps 2 ( $R^1R^2\text{NH} = \text{phenethylamine}$ ).

#### Step 1: Methyl 4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (209)

**[0266]** To a degazed solution of **208** (300 mg, 0.75 mmol) in MeOH (35 mL) was added 10% Pd/C (24 mg, 0.023 mmol). The reaction mixture was stirred under a 1 atm pressure of  $\text{H}_2$  at room temperature for 20 h then it was purged with  $\text{N}_2$ . The palladium was removed by filtration through celite and the reaction mixture was concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/ $\text{CH}_2\text{Cl}_2$ : 4/96) to afford the title compound **209** (135 mg, 0.37 mmol, 50% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.08 (d,  $J = 8.1$  Hz, 2H), 7.46 (d,  $J = 8.1$  Hz, 2H), 7.50-7.15 (m, 6H), 4.85-4.65 (m, 2H), 3.98 (s, 3H), 3.82-3.62 (m, 2H), 3.05-2.85 (m, 2H).

Step 2: *N*-(2-Amino-phenyl)-4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide (**210**)

**[0267]** The title compound **210** was obtained from **209** in 2 steps following the same procedure as in Example 1, steps 4 and 5. <sup>1</sup>H NMR: (300 MHz, acetone-d<sub>6</sub>) δ (ppm): 9.03 (s, 1H), 8.17-7.87 (m, 3H), 7.49 (dd, J = 19.2, 8.2 Hz, 2H), 7.32-7.03 (m, 6H), 6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-6.30 (m, 2H), 4.72 (t, J = 6.3 Hz, 1H), 4.65-4.56 (m, 1H), 3.67-3.51 (m, 2H), 2.95-2.80 (m, 2H).

**Scheme 27****Example 138**Step 1: Methyl 4-[(4,6-dimethoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (**211**)

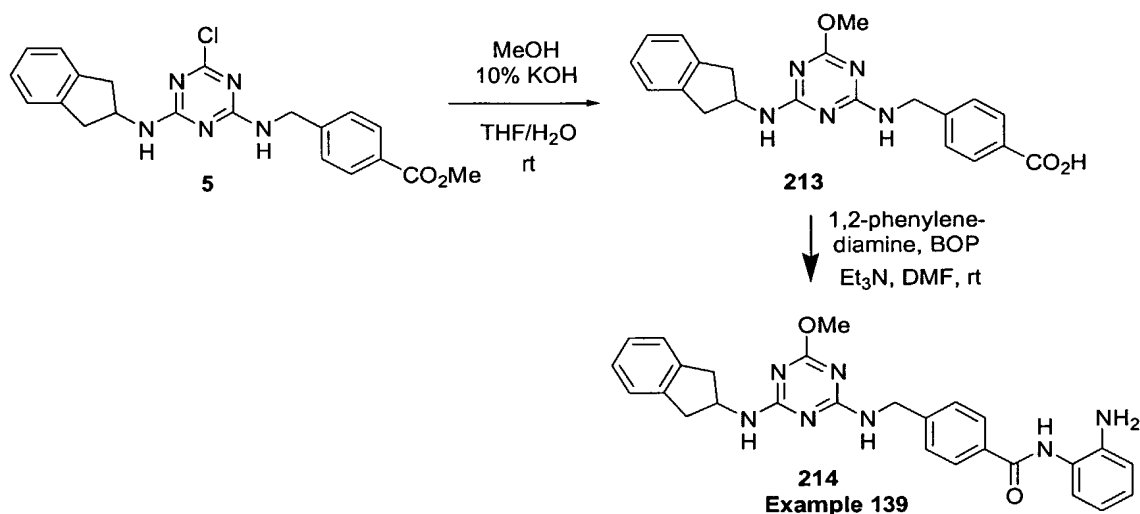
**[0268]** In a 75ml sealed flask, a stirred suspension of 2-chloro-4,6-dimethoxy-1,3,5-triazine (540 mg, 3.08 mmol), methyl 4-(aminomethyl)benzoate.HCl **2** (689 mg, 3.42 mmol), *i*-Pr<sub>2</sub>NEt (1.49 ml, 8.54 mmol) in anhydrous THF (30 ml) was warmed at 80°C for 5 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH<sub>4</sub>Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH<sub>2</sub>Cl<sub>2</sub>: 10/90→30/70) to afford the title compound **211** (870 mg, 2.86 mmol, 93% yield) as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): AB

system ( $\delta_A = 8.01$ ,  $\delta_B = 7.39$ ,  $J_{AB} = 8.5$  Hz, 4H), 6.08-6.00 (m, 1H), 4.73 (d,  $J = 6.3$  Hz, 2H), 3.95 (s, 6H), 3.92 (s, 3H).

**[0269]** The title compound **212** was obtained from **211** in 2 steps following the same procedure as Example 1, steps 4 and 5.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$  +  $\Sigma$  DMSO- $d_6$ )  $\delta$  (ppm): 9.58 (bs, 1H), 8.27 (t,  $J = 6.3$  Hz, 1H), AB system ( $\delta_A = 8.04$ ,  $\delta_B = 7.53$ ,  $J_{AB} = 8.4$  Hz, 4H), 7.31 (d,  $J = 6.9$  Hz, 1H), 7.02 (td,  $J = 7.6$ , 1.6 Hz, 1H), 6.88 (dd,  $J = 7.9$ , 1.4 Hz, 1H), 6.68 (td,  $J = 7.6$ , 1.4 Hz, 1H), 4.86-4.78 (m, 2H), 4.69 (d,  $J = 6.3$  Hz, 2H), 3.90 and 3.89 (2s, 6H). HRMS (calc.): 380.1597, (found): 380.1601.

Step 2: *N*-(2-Amino-phenyl)-4-[(4,6-dimethoxy-[1,3,5]-triazin-2-yl-amino)-methyl]-benzamide (**212**)

### Scheme 28



### Example 139

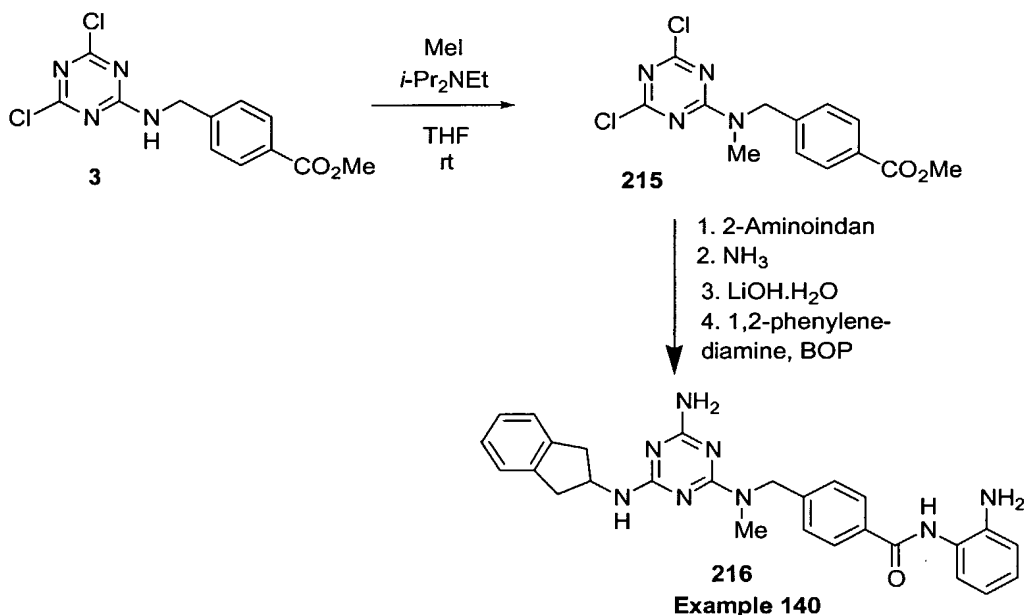
Step 1: 4-[(6-(2-Indanyl-amino)-4-methoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (**213**)

**[0270]** To a stirred solution at room temperature of **5** (300 mg, 0.73 mmol) in a mixture of MeOH/THF (10 ml/5 ml) was added an aqueous solution of KOH (10%, 5 ml). After 3 days, the reaction mixture was concentrated on the rotavap, diluted in water and acidified with 1N HCl until pH 5-6 in order to get a white precipitate. After 15 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **213** (282 mg, 0.72 mmol, 98% yield) as a white solid. MS:  $m/z = 392.1$   $[\text{MH}]^+$ .

Step 2: N-(2-amino-phenyl)-4-[[6-(2-indanyl-amino)-4-methoxy-[1,3,5]-triazin-2-yl-amino]-methyl]-benzamide (214)

**[0271]** The title compound **214** was obtained from **213** in one step following the same procedure as Example 1, step 5.  $^1\text{H}$  NMR (300 MHz, acetone- $\text{d}_6$  +  $\square$  DMSO- $\text{d}_6$ )  $\delta$  (ppm): mixture of rotamers, 9.69-9.53 (m, 1H), AB system ( $\delta_{\text{A}} = 8.04$ ,  $\delta_{\text{B}} = 7.52$ ,  $J_{\text{AB}} = 7.8$  Hz, 4H), 7.80-7.60 (m, 1H), 7.45-7.10 (m, 6H), 7.01 (t,  $J = 7.6$  Hz, 1H), 6.88 (d,  $J = 8.2$  Hz, 1H), 6.68 (t,  $J = 7.6$  Hz, 1H), 4.92-4.60 (m, 5H), 3.90-3.78 (m, 3H), 3.35-3.22 (m, 2H), 3.02-2.83 (m, 2H). HRMS (calc.): 481.2226, (found): 481.2231.

**Scheme 29**



**Example 29**

Step 1: Methyl 4-[(4,6-dichloro-[1,3,5]triazin-2-yl-N-methyl-amino)-methyl]-benzoic ester (216)

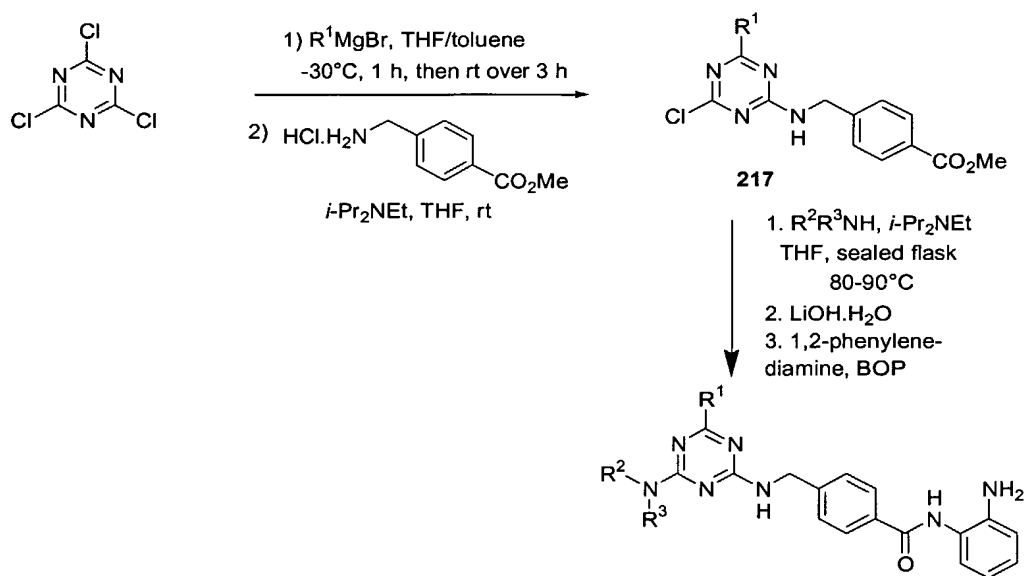
**[0272]** To a stirred suspension at room temperature of NaH (95%, 81 mg, 3.19 mmol) in anhydrous THF (10 ml) under nitrogen were successively added a solution of **3** (500 mg, 1.60 mmol) in anhydrous THF (10 ml) and MeI (298  $\mu\text{l}$ , 4.79 mmol). After 16 h, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel

(AcOEt/hexane: 10/90→20/80) to afford the title compound **215** (200 mg, 0.61 mmol, 38% yield) as a white crystalline solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): AB system ( $\delta_A = 8.04$ ,  $\delta_B = 7.31$ ,  $J_{AB} = 8.2$  Hz, 4H), 4.93 (s, 2H), 3.93 (s, 3H), 3.18 (s, 3H).

Step 2: 4-[[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-N-methyl-amino]-methyl]-N-(2-amino-phenyl)-benzamide (**216**)

**[0273]** The title compound **216** from **215** in 4 steps was obtained following the same procedure as Example 1, Pathway B steps 2-5.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 9.11 (bs, 1H), 8.03 (d,  $J = 8.0$  Hz, 2H), 7.43 (bs, 2H), 7.33 (d,  $J = 7.7$  Hz, 1H), 7.28-7.09 (m, 4H), 7.04 (td,  $J = 7.6$ , 1.5 Hz, 1H), 6.90 (dd,  $J = 8.0$ , 1.4 Hz, 1H), 6.71 (td,  $J = 7.5$ , 1.3 Hz, 1H), 6.25-6.05 (m, 1H), 5.82 and 5.64 (2bs, 2H), 5.00-4.56 (m, 5H), 3.42-2.76 (m, 7H). HRMS (calc.): 480.2386, (found): 480.2377.

### Scheme 30



**Example 141** **218**:  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2\text{R}^3\text{N} = 2\text{-indanyl-amino}$

### Example 141:

Step 1: Methyl 4-[(4-chloro-6-methyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (**217**)

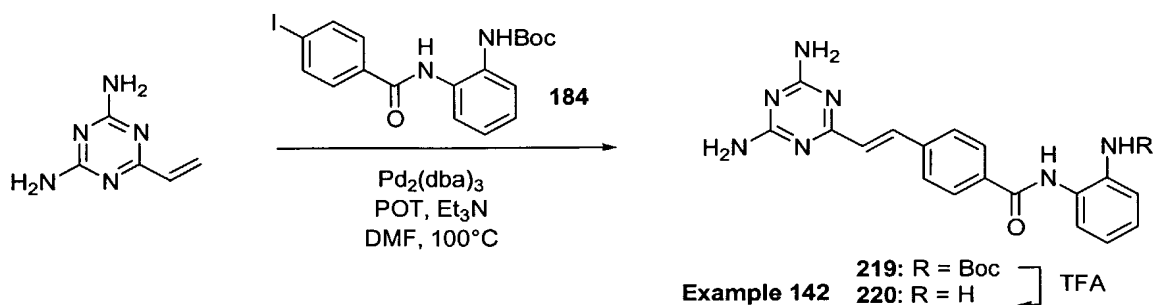
**[0274]** To a stirred solution at -30°C of cyanuric chloride **1** (2.00 g, 10.85 mmol) in anhydrous THF (100 ml) under nitrogen was slowly added a solution of  $\text{MeMgBr}$  (17 ml, 23.86 mmol, 1.4 M in anhydrous THF/toluene). After 1 h, the reaction mixture was allowed to warm to room temperature over 3 h. Then, methyl 4-(aminomethyl)benzoate.HCl **2** (2.08 g, 10.30 mmol) and  $i\text{-Pr}_2\text{NEt}$  (3.78 ml,

21.69 mmol) were added, respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with  $\text{AcOEt}$ . After separation, the organic layer was successively washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ( $\text{AcOEt}/\text{CH}_2\text{Cl}_2$ : 10/90 $\rightarrow$ 15/85) to afford the title compound **217** (780 mg, 2.67 mmol, 25% yield) as a yellow powder.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): mixture of rotamers, 2 AB system ( $\delta_{\text{A}} = 8.03$ ,  $\delta_{\text{A}'} = 8.02$ ,  $\delta_{\text{B}} = 7.39$ ,  $\delta_{\text{B}'} = 7.38$ ,  $J = 8.5$  Hz, 4H), 6.28-6.08 (2 m, 1H), 4.76 and 4.74 (2d,  $J = 6.3$  Hz, 2H), 3.92 (s, 3H), 2.46 and 2.42 (2s, 3H).

Step 2: *N*-(2-amino-phenyl)-4-[(6-(2-indanyl-amino)-4-methyl-[1,3,5]-triazin-2-yl-amino)-methyl]-benzamide (218)

**[0275]** The title compound **218** was obtained from **217** in 3 steps following the same procedure as Example 1, steps 3-5.  $^1\text{H}$  NMR (300 MHz, acetone- $\text{d}_6 + \Sigma$  DMSO- $\text{d}_6$ )  $\delta$  (ppm): mixture of rotamers, 9.62-9.50 (m, 1H), 8.04 (d,  $J = 8.0$  Hz, 2H), 7.68-7.37 (m, 3H), 7.33 (d,  $J = 7.7$  Hz, 1H), 7.28-7.07 (m, 5H), 7.02 (t,  $J = 7.4$  Hz, 1H), 6.89 (d,  $J = 7.9$  Hz, 1H), 6.69 (t,  $J = 7.4$  Hz, 1H), 4.92-4.60 (m, 5H), 3.35-3.10 (m, 2H), 3.02-2.82 (m, 2H), 2.25-2.12 (m, 3H).

### Scheme 31



### Example 142

Step 1: (2-{4-[2-(4,6-Diamino-[1,3,5]triazin-2-yl)-vinyl]-benzoylamino}-phenyl)-carbamic tert-butyl ester (219)

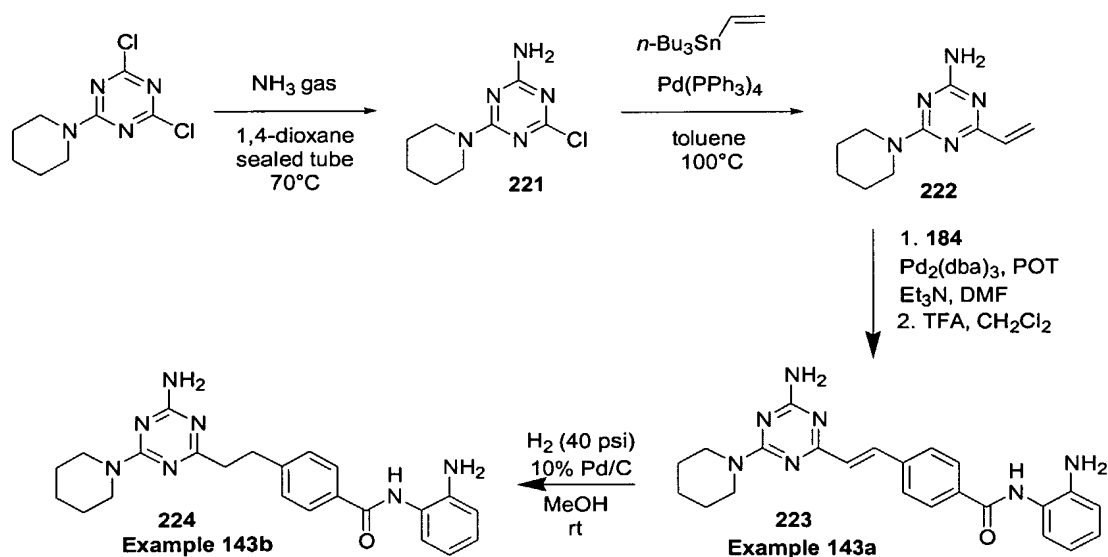
**[0276]** To a degazed solution of **184** (40 mg, 0.091 mmol) and 2-vinyl-4,6-diamino-1,3,5-triazine (11 mg, 0.083 mmol) in dry DMF (1 mL) was added tri-*o*-tolylphosphine (POT) (1.5 mg, 0.005 mmol) followed by  $\text{Et}_3\text{N}$  (46  $\mu\text{L}$ , 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.0025 mmol). The solution was heated at  $100^\circ\text{C}$  for 16h. Then, DMF was removed under reduced

pressure. The reaction mixture was partitioned between AcOEt and a solution of sat.  $\text{NH}_4\text{Cl}$ . After separation, the organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ( $\text{MeOH}/\text{CH}_2\text{Cl}_2$ : 5/95) to afford the title compound **219** (25 mg, 0.056 mmol, 67% yield).  $^1\text{H}$  NMR (300 MHz, Acetone- $d_6$ )  $\delta$  (ppm): 8.27 (s, 1H), 8.06 (d,  $J$  = 8.1 Hz, 2H), 7.96 (d,  $J$  = 15.9 Hz, 1H), 7.79 (d,  $J$  = 8.1 Hz, 2H), 7.76-7.69 (m, 1H), 7.62-7.55 (m, 1H), 7.26-7.15 (m, 2H), 6.90 (d,  $J$  = 15.9 Hz), 6.21 (s, 4H), 1.50 (s, 9H).

Step 2: *N*-(2-Amino-phenyl)-4-[2-(4,6-diamino-[1,3,5]triazin-2-yl)-vinyl]-benzamide (**220**)

**[0277]** To a stirred solution at room temperature of **219** (25 mg, 0.056 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was added TFA (0.3 mL, 4.3 mmol). After 30 min, a solution of sat.  $\text{NaHCO}_3$  was slowly added until pH 8 is reached,  $\text{CH}_2\text{Cl}_2$  was removed under reduced pressure, AcOEt was added, and the phases were separated. The organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel ( $\text{MeOH}/\text{CH}_2\text{Cl}_2$ : 10/90) to afford the title compound **220** (19 mg, 0.054 mmol, 98% yield).  $^1\text{H}$  NMR: (300 MHz, acetone- $d_6$ )  $\delta$  (ppm): 8.33, 8.13 (2d,  $J$  = 7.5 Hz, 1H), 8.22 (d,  $J$  = 15.9 Hz, 1H), 8.01 (d,  $J$  = 8.1 Hz, 2H), 7.84 (d,  $J$  = 8.1 Hz, 2H), 7.38-6.96 (m, 2H), 7.03 (d,  $J$  = 15.9 Hz, 1H), 6.94-6.62 (m, 2H).

**Scheme 32**



**Example 143a****Step 1: 2-Amino-4-chloro-6-piperidin-1-yl-[1,3,5]triazin (221)**

**[0278]** Ammonia was bubbled for 5 min in a solution of 2,4-dichloro-6-piperidin-1-yl-[1,3,5]triazine (500 mg, 2.15 mmol) in dry 1,4-dioxane (20 mL). The solution was heated at 70°C for 16h in a sealed tube. The reaction mixture was allowed to cool to room temperature, and partitioned between AcOEt and a solution of sat. NH<sub>4</sub>Cl. After separation, the organic layer was washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford the title compound **221** (453 mg, 2.12 mmol, 98% yield). LRMS: [MH]<sup>+</sup> = 214.1.

**Step 2: 2-Amino 4-piperidin-1-yl-6-vinyl-[1,3,5]triazin (222)**

**[0279]** To a solution of **221** (358 mg, 1.68 mmol) in dry toluene (7 mL) was added tributyl(vinyl)tin (514 µL, 1.76 mmol) followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (97 mg, 0.084 mmol) and the reaction mixture was heated at 100°C for 16h in a sealed tube. Then, the reaction mixture was allowed to cool to room temperature, concentrated, and purified directly by flash chromatography on silica gel (AcOEt/hexane: 10/90→30/70) to afford the title compound **222** (containing tributyltin chloride).

**Steps 3: N(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-vinyl]-benzamide (223)**

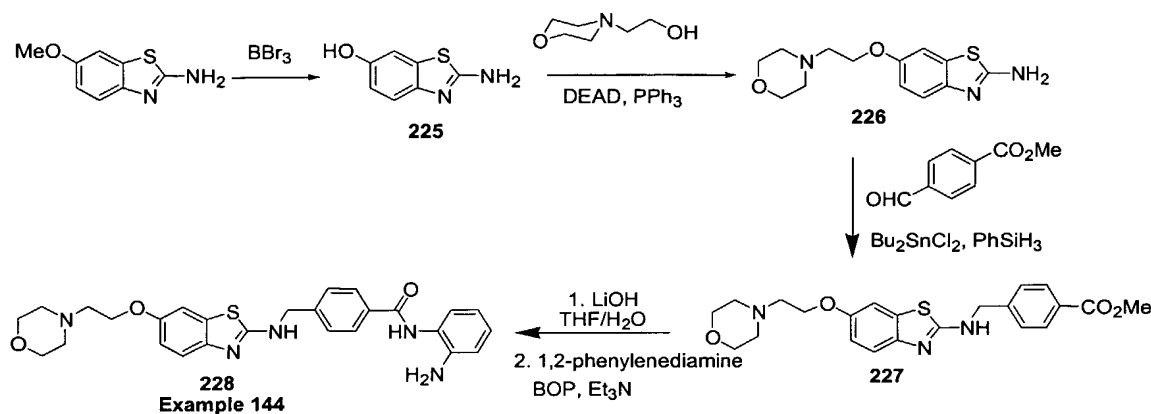
**[0280]** The title compound **223** was obtained from **222** in 2 steps following the same procedure as in scheme 31, steps 1 and 2. <sup>1</sup>H NMR: (300 MHz, DMSO-d<sub>6</sub>) δ (ppm): 9.69 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 16.0 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.04-6.92 (m, 1H), 6.91 (d, J = 16 Hz, 1H), 6.85-6.68 (m, 3H), 6.60 (t, J = 7.2 Hz, 1H), 4.93 (s, 2H), 3.77 (s, 4H), 1.63 (s, 2H), 1.52 (s, 4H).

**Example 143b****Step 4: N(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-ethyl]-benzamide (224)**

**[0281]** To a solution of **223** (18 mg, 0.043 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 0.021 mmol). The reaction mixture was shaken under a pressure of H<sub>2</sub> (40 psi) at room temperature for 16 h using an hydrogenation apparatus. Then, the reaction mixture was purged with N<sub>2</sub>, filtered through celite, and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub>: 2/98→4/96) to afford the title compound **224** (10 mg, 0.024 mmol, 56% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ (ppm): 7.82 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 6.89-6.79 (m, 2H), 7.80-6.90 (m, 1H), 3.76 (s, 4H), 3.13 (t, J = 8.1 Hz, 2H), 2.88 (t, J = 8.1 Hz, 2H), 1.90-1.40 (m, 10H).



## Scheme 33



## Example 144

Step 1: 2-Amino-benzothiazol-6-ol (**225**):

[0282] A suspension of 2-amino-6-methoxybenzothiazole (5.00 g, 27.8 mmol) in dichloromethane (70 mL) was cooled to  $0^\circ\text{C}$  under nitrogen and boron tribromide (3.93 mL, 41.6 mmol) was added dropwise. The light yellow mixture was stirred for 3 h, allowing to warm-up slowly from  $0^\circ\text{C}$  to  $10^\circ\text{C}$ . The reaction was slowly quenched by dropwise addition of methanol and after stirring overnight at room temperature, the white solid was collected by filtration (6.04 g, 88% yield). This hydrobromic salt was dissolved in water, washed with ethyl acetate, and neutralized with a saturated aqueous solution of  $\text{NaHCO}_3$ . The resulting crystals were collected by filtration and dried in the oven at  $135^\circ\text{C}$  for 1 h to afford the title compound **225** as colorless crystals (3.63 g, 79% yield).  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.27 (d,  $J=8.8$  Hz, 1H), 7.08 (d,  $J=2.2$  Hz, 1H), 6.80 (dd,  $J=8.4$ , 2.2 Hz, 1H).

Step 2: 6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamine (**226**)

[0283] To a solution of benzothiazole **225** (3.62 g, 21.8 mmol) in THF at room temperature under nitrogen, were successively added 4-(2-hydroxyethyl)morpholine (3.17 mL, 26.1 mmol), triphenylphosphine (7.43 g, 28.3 mmol) followed by a dropwise addition of diethyl azodicarboxylate (4.46 mL, 28.3 mmol). The solution was stirred for 3.5 h and THF was partially removed *in vacuo*. The mixture was partitioned between ethyl acetate and  $\text{H}_2\text{O}$ . The combined organic layers were extracted with 1N HCl. The combined acidic extracts were neutralized using a saturated aqueous solution of  $\text{NaHCO}_3$  and the precipitate was dissolved with ethyl acetate. These combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated. The filtrate was concentrated to afford the title compound **226** (5.83 g, 96% yield) as a light yellow oil.  $^1\text{H}$  NMR: (Acetone- $d_6$ )  $\delta$

(ppm): 7.37 (d, J=8.8 Hz, 1H), 7.34 (d, J=2.6 Hz, 1H), 6.94 (dd, J=8.8, 2.6 Hz, 1H), 6.60 (bs, 2H), 4.19 (t, J=6.2 Hz, 2H), 3.70-3.67 (m, 4H), 2.90 (s, 2H), 2.81 (t, J=6.2 Hz, 2H), 2.62-2.58 (m, 4H).

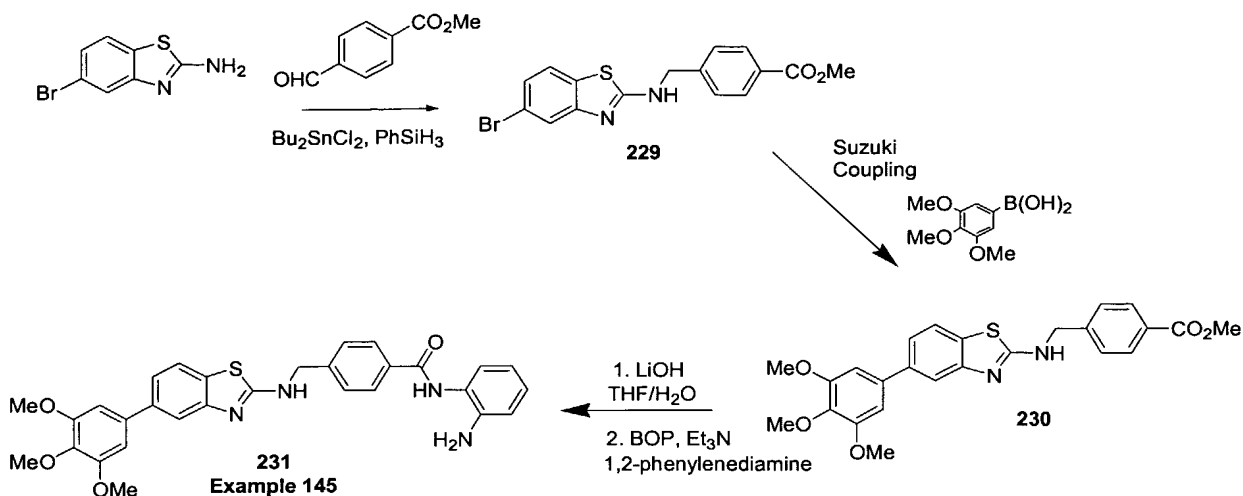
Step 3: 4-[[6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl]-benzoic acid methyl ester (227):

**[0284]** To a round-bottom flask containing benzothiazole **226** (5.80 g, 20.8 mmol) was added methyl 4-formylbenzoate (5.11 g, 31.1 mmol), followed by THF (8 mL), dibutyltin dichloride (315 mg, 1.04 mmol) and dropwise addition of phenylsilane (3.24 mL, 31.1 mmol). The resulting mixture was stirred overnight at room temperature under nitrogen. The mixture was diluted in ethyl acetate and filtered. The filtrate was partitioned between ethyl acetate and water and the combined organic layers were washed with 1N HCl. The combined acidic layers were neutralized using a saturated aqueous solution of NaHCO<sub>3</sub> and the precipitate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting crude was purified by flash chromatography using MeOH/CHCl<sub>3</sub> (10:90) to afford **227** (3.69 g, 42% yield). <sup>1</sup>H NMR: (Acetone-d<sub>6</sub>) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H).

Step 4: N-(2-Amino-phenyl)-4-[[6-(2-morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl]-benzamide (228):

**[0285]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **228** was obtained (958 mg, 46%) as a colorless solid. <sup>1</sup>H NMR: (CD<sub>3</sub>OD) δ (ppm): 8.04 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.8 Hz, 1H), 7.31 (d, J=2.5 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 6.97 (dd, J=8.8, 2.5 Hz, 2H), 6.84 (t, J=7.4 Hz, 1H), 4.78 (s, 2H), 4.21 (t, J=5.2 Hz, 2H), 3.81-3.77 (m, 4H), 2.87 (t, J=5.5, 2H), 2.69-3.66 (m, 4H).

## Scheme 34



## Example 145

Step 1: 4-[(5-Bromo-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (**229**):

**[0286]** Following the procedure described in Example 144, step 3, but substituting the 2-amino-6-bromobenzothiazole for **226**, the title compound **229** was obtained in 56% yield.  $^1\text{H}$  NMR: ( $\text{DMSO}-d_6$ )  $\delta$  (ppm): 8.78 (t,  $J=5.9$  Hz, 1H), 8.01 (d,  $J=8.2$  Hz, 2H), 7.99 (s, 1H), 7.56 (d,  $J=8.2$  Hz, 2H), 7.43-7.34 (m, 2H), 4.74 (d,  $J=5.9$  Hz, 2H), 3.90 (s, 3H).

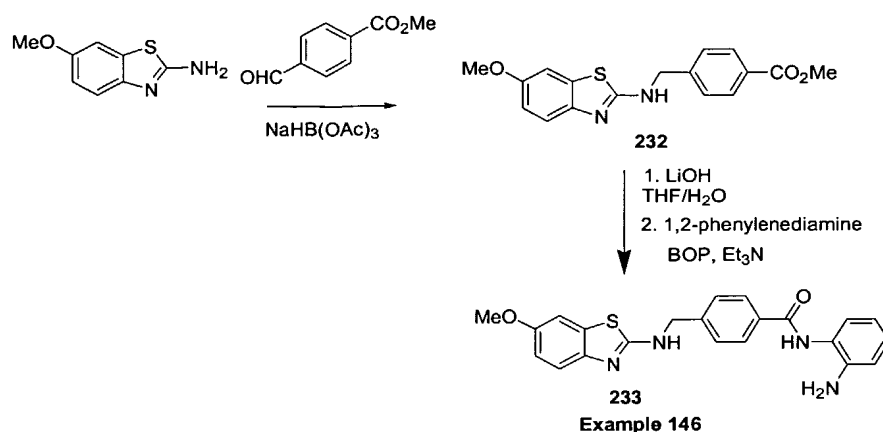
Step 2: 4-[(5-(3,4,5-Trimethoxy-phenyl)-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (**230**):

**[0287]** Following the procedure described in Example 15, step 1, but substituting **229** for **140**, the title compound **230** was obtained in 44% yield as colorless crystals.  $^1\text{H}$  NMR: ( $\text{DMSO}-d_6$ )  $\delta$  (ppm): 8.73 (t,  $J=5.7$  Hz, 1H), 8.11 (d,  $J=1.8$  Hz, 1H), 8.02 (d,  $J=8.4$  Hz, 2H), 7.63-7.57 (m, 3H), 7.48 (d,  $J=8.4$  Hz, 1H), 6.97 (s, 2H), 4.77 (d,  $J=5.7$  Hz, 2H), 3.92 (m, 6H), 3.90 (s, 3H), 3.74 (s, 3H).

Step 3: *N*-(2-Amino-phenyl)-4-[(5-(3,4,5-trimethoxy-phenyl)-benzothiazol-2-ylamino)-methyl]-benzamide (**231**):

**[0288]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **231** was obtained in 69% yield.  $^1\text{H}$  NMR: ( $\text{Acetone}-d_6$ )  $\delta$  (ppm): 8.31 (d,  $J=7.9$  Hz, 2H), 8.20 (d,  $J=7.5$  Hz, 1H), 8.13 (s, 1H), 7.73-7.58 (m, 3H), 7.63 (d,  $J=7.5$  Hz, 2H), 7.48-7.43 (m, 2H), 7.05 (s, 2H), 4.98 (s, 2H), 4.00 (s, 6H), 3.84 (s, 3H).

## Scheme 35



## Example 146

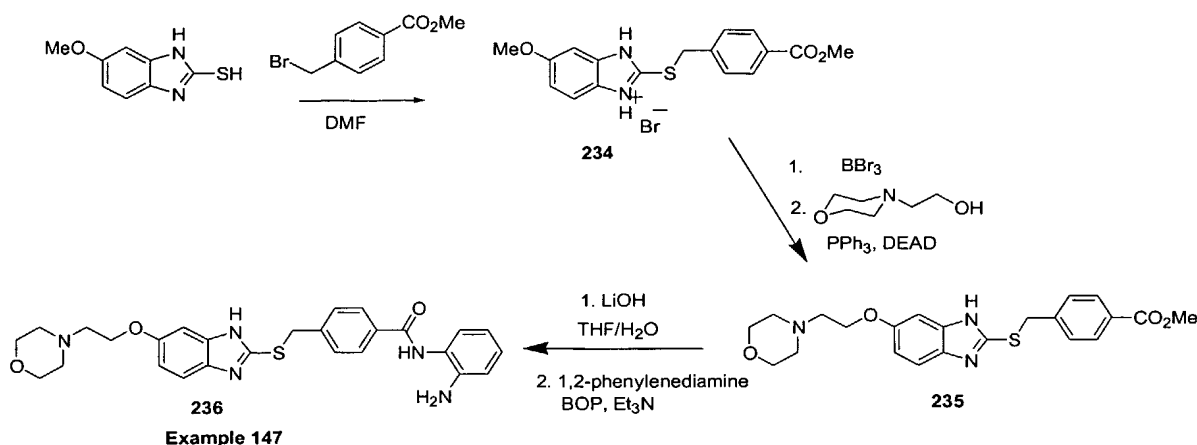
Step 1: 4-[(6-Methoxy-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (**232**):

**[0289]** To a solution of 2-amino-6-methoxybenzothiazole (2.00 g, 11.1 mmol) in a mixture of dichloroethane (20 mL) and THF (20 mL), were successively added methyl 4-formylbenzoate (1.82 g, 11.1 mmol), sodium triacetoxyborohydride (3.53 g, 16.7 mmol) and acetic acid (1.27 mL, 22.2 mmol). The mixture was stirred over 2 days and was quenched by adding aqueous saturated solution of  $\text{NaHCO}_3$ . The mixture was poured in a separating funnel containing water and was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc/ hexane (20:80 to 30:70) to afford the title compound **232** (1.85g, 51% yield). <sup>1</sup>H NMR: (Acetone-d<sub>6</sub>)  $\delta$  (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H).

Step 2: N-(2-Amino-phenyl)-4-[(6-methoxy-benzothiazol-2-ylamino)-methyl]-benzamide(**233**):

**[0290]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **233** was obtained in 19% yield as a light beige solid. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>)  $\delta$  (ppm): 9.68 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.00 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.39 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.21 (d, J=6.6 Hz, 1H), 7.05 (t, J=6.3 Hz, 1H), 7.00 (d, J=1.4 Hz, 1H), 6.88 (dd, J=8.8, 2.7 Hz, 1H), 6.86 (dd, J=8.0, 1.4 Hz, 1H), 6.65 (td, J=7.4, 1.4 Hz, 1H), 4.95 (s, 2H), 4.70 (d, J=5.8 Hz, 2H), 3.79 (s, 3H).

## Scheme 36



## Example 147

Step 1: 4-(6-Methoxy-1H-benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester hydrobromide (234):

**[0291]** To a solution of methyl 4-(bromomethyl)benzoate (2.51g, 11.0 mmol) in DMF (50 mL) was added 5-methoxy-2-benzimidazolethiol (1.98g, 11.0 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated *in vacuo*. The residue was suspended in ethyl acetate and the hydrobromide salt was collected by filtration to afford the title compound **234** (4.10g, 91% yield) as a colorless solid. <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 7.90 (d, J= 8.2 Hz, 2H), 7.55 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 1H), 7.03 (s, 1H), 6.94 (d, J= 8.2 Hz, 1H), 4.65 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H).

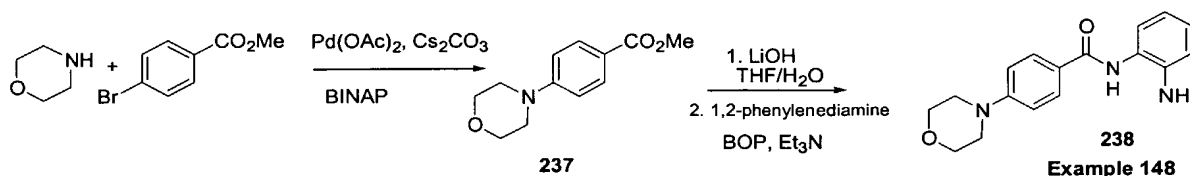
Step 2:: 4-[6-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (235):

**[0292]** Following the procedure described in Example 144, step 1, 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound **235** was obtained in 37% yield. <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ (ppm): 8.04-8.00 (m, 2H), 7.77-7.72 (m, 1H), 7.69-7.59 (m, 1H), 7.56-7.49 (m, 2H), 6.96-6.90 (m, 1H), 4.68 (s, 2H), 4.31-4.16 (m, 4H), 3.97 (s, 3H), 3.98-3.91 (m, 2H), 3.82-3.72 (m, 2H), 2.75-2.47 (m, 4H).

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyl]-benzamide (236):

**[0293]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **236** was obtained in 11% yield.  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.89 (d,  $J$ = 8.2 Hz, 2H), 7.45 (d,  $J$ = 8.2 Hz, 2H), 7.28 (d,  $J$ = 8.5 Hz, 1H), 7.19-7.06 (m, 3H), 6.93-6.79 (m, 3H), 4.55 (s, 2H), 4.18 (t,  $J$ = 6.3 Hz, 2H), 3.65-3.62 (m, 4H), 2.51 (t,  $J$ = 6.6 Hz, 2H), 2.46-2.42 (m, 4H).

### Scheme 37



### Example 148

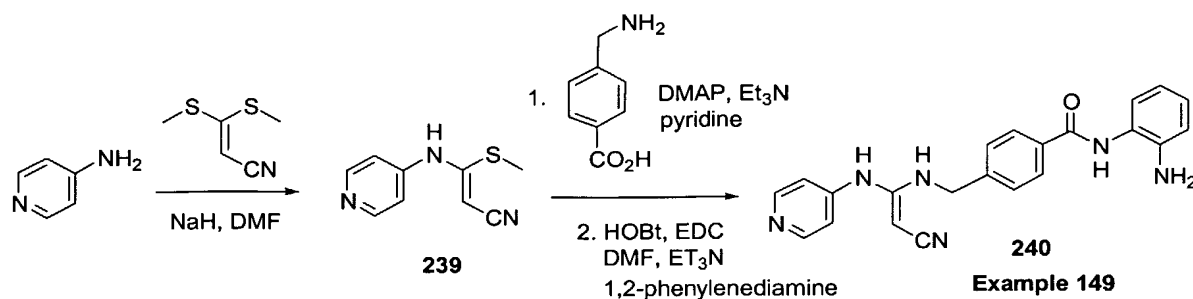
Step 1: 4-Morpholin-4-yl-benzoic acid methyl ester (237):

**[0294]** A flame-dried pressure vessel was charged with cesium carbonate (912 mg, 2.80 mmol) and toluene (8 mL) and the flasked was purged with nitrogen. Palladium acetate (9.0 mg, 0.004 mmol) and *rac*-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (37 mg, 0.06 mmol). The mixture was degassed and heated at 100°C for 18 h. It was allowed to cool to room temperature and was filtered through celite, rinsed with ethyl acetate and partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of  $\text{NaHCO}_3$ , brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound **237** (443 mg, 100% yield).  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ )  $\delta$  (ppm): 8.02 (d,  $J$ =9.2 Hz, 2H), 6.95 (d,  $J$ =8.8 Hz, 2H), 3.95 (s, 4H), 3.92 (s, 3H), 3.38-3.35 (m, 4H).

Step 2: N-(2-Amino-phenyl)-4-morpholin-4-yl-benzamide (238):

**[0295]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **238** was obtained in 33 % yield.  $^1\text{H}$  NMR: ( $\text{DMSO}-d_6$ )  $\delta$  (ppm): 7.20 (d,  $J$ = 7.9 Hz, 1H), 7.07 (d,  $J$ = 8.8 Hz, 2H), 7.01 (t,  $J$ = 7.0 Hz, 1H), 6.83 (d,  $J$ = 7.9 Hz, 1H), 6.65 (t,  $J$ = 7.5 Hz, 1H), 4.90 (s, 2H), 3.81-3.79 (m, 4H), 3.32-3.28 (m, 4H).

## Scheme 38



## Example 149

Step 1: 3-Methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (**239**)

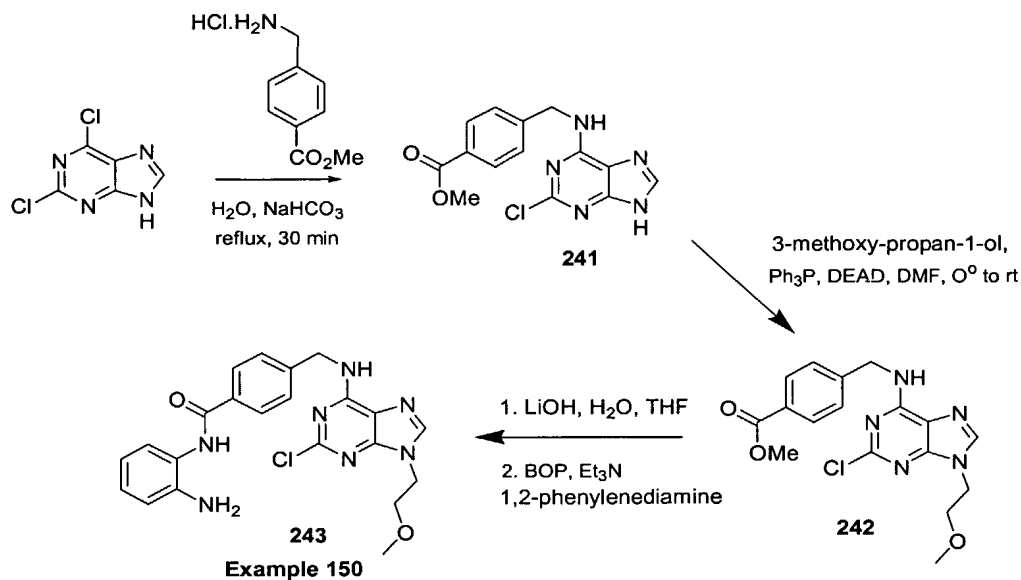
**[0296]** To a solution of pyridin-4-ylamine (1.0 g, 11.0 mmol) and 3,3-Bis-methylsulfanyl-acrylonitrile (2.05 g, 12.6 mmol) in DMF at room temperature, was added powdered 4A molecular sieves. The mixture was stirred for 1 hr. Subsequently the mixture was cooled to 0 °C, 60% NaH dispersion in oil (0.92 g, 23.0 mmol) was added portionwise over 1 hr. and it was stirred at 0 °C for an additional 2 hrs. The cold bath was removed and the mixture was stirred at room temperature for 20 hrs. DMF was removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 25% MeOH/EtOAc) to afford the desired product as an off-white solid (1.9 g, 89%).

Step 2: N-(2-Amino-phenyl)-4-[(2-cyano-1-(pyridin-4-ylamino)-vinylamino)-methyl]-benzamide (**240**)

**[0297]** To a mixture of 3-methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (0.2 g, 1.0 mmol), 4-aminomethyl-benzoic acid (0.173 g, 1.14 mmol), DMAP (1 mg) and Et<sub>3</sub>N (0.14 ml, 1.0 mmol) was added dry pyridine (0.5 ml). The resulting stirring mixture was heated to 55 °C for 4.5 hrs., additional Et<sub>3</sub>N (0.14 ml) was added and mixture was heated from 75 °C to 90 °C over a period of ~30 hrs. When the reaction was complete, pyridine was partially removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 20% MeOH/EtOAc) to afford the desired product as an off-white solid (130 mg, 44%).

**[0298]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **240** was obtained in 33 % yield. <sup>1</sup>H NMR: (300 MHz, DMSO-d<sub>6</sub>) δ (ppm): 9.69 (br, 2H), 8.48 (br, 3H), 8.03 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.29 (br, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 4.96 (br, 2H), 4.62 (d, J = 5.7 Hz, 2H).

## Scheme 39



## Example 150

Step 1: 4-[(2-Chloro-9H-purin-6-ylamino)-methyl]-benzoic acid methyl ester (**241**)

**[0299]** A suspension of 2,6-dichloro-9H-purine (1 g, 5.29 mmol), 4-aminomethyl-benzoic acid methyl ester hydrochloride (1.2 equiv., 1.28 g) and  $\text{NaHCO}_3$  (2.1 equiv., 935 mg) in water was heated at  $100^\circ\text{C}$ . The homogeneous solution thus formed was refluxed 30 min. The resulting white precipitate was filtered, washed with cold water and dried under vacuum giving the title compound **241** (1 g, 3.14 mmol, 60%). LRMS calc: 317.7, found: 318.3 (MH)<sup>+</sup>.

Step 2: 4-[(2-Chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylamino)-methyl]-benzoic acid methyl ester (**242**)

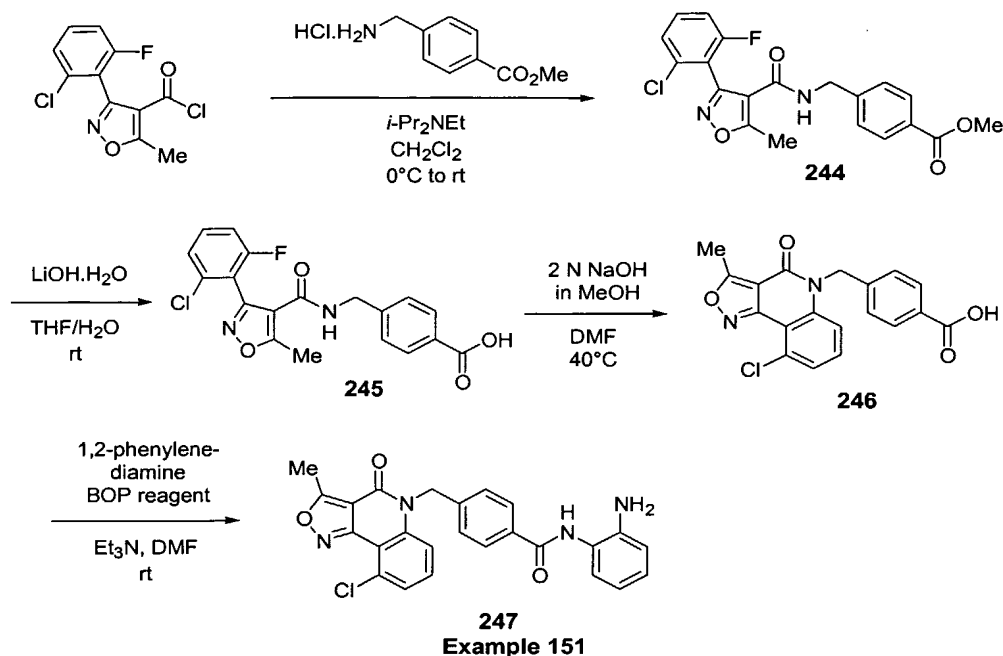
**[0300]** Following the procedure described in Example 144, step 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound **242** was obtained in 41% yield.

Step 3: N-(2-Amino-phenyl)-4-[(2-chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylamino)-methyl]-benzamide (**243**):

**[0301]** Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **243** was obtained in 85% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 9.64 (s, 1H), 8.94 (bs, 1H), 8.18 (s, 1H), 7.96 (d,  $J = 7.8$  Hz, 2H), 7.52 (d,  $J = 7.8$  Hz, 2H), 7.21 (d,  $J = 7.7$  Hz, 1H), 7.01 (dd,  $J = 7.3, 8.0$  Hz, 1H), 6.81 (d,  $J = 8.0$  Hz, 1H), 6.62 (dd,  $J = 7.3, 7.7$  Hz, 1H), 4.91 (bs, 2H), 4.78 (bs, 2H), 4.18 (m, 2H), 3.70 (m, 2H), 3.26 (s, 3H).



## Scheme 40



## Example 151

Step 1: Methyl 4-[(3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl)-amino-methyl]-benzoic acid ester (**244**)

**[0302]** To a stirred suspension at 0°C of methyl 4-(aminomethyl)benzoate.HCl **2** (809 mg, 4.01 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (25 ml) under nitrogen were successively added *i*-Pr<sub>2</sub>NEt (1.91 ml, 10.95 mmol) and 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (1.00 g, 3.65 mmol). After 45 min, the reaction mixture was allowed to warm up to room temperature for 3 h. Then, the reaction mixture was concentrated, diluted with AcOEt, and successively washed with sat. NH<sub>4</sub>Cl, H<sub>2</sub>O, sat. NaHCO<sub>3</sub>, H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to afford the title compound **244** (1.50 g, quantitative yield) as a colorless sticky foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.93 (d, *J* = 7.9 Hz, 2H), 7.46-7.35 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.15-7.05 (m, 3H), 5.49 (bs, 1H), 4.46 (d, *J* = 5.7 Hz, 2H), 3.92 (s, 3H), 2.80 (s, 3H).

Step 2: 4-[(3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl)-amino-methyl]-benzoic acid (**245**)

**[0303]** To a stirred solution at room temperature of **244** (1.45 g, 3.60 mmol) in THF (20 ml) was added a solution of LiOH.H<sub>2</sub>O (453 mg, 10.80 mmol) in water (20 ml). After 20 h, the reaction

mixture was concentrated, diluted with water and acidified with 1N HCl until pH 6 in order to get a white precipitate. After 10 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **245** (1.23 g, 3.15 mmol, 88% yield) as a white solid.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm): 8.69 (t,  $J$  = 5.9 Hz, 1H), 7.91 (d,  $J$  = 7.9 Hz, 2H), 7.70-7.58 (m, 1H), 7.51 (d,  $J$  = 7.9 Hz, 1H), 7.45-7.30 (m, 3H), 4.44 (d,  $J$  = 5.7 Hz, 2H), 2.72 (s, 3H).

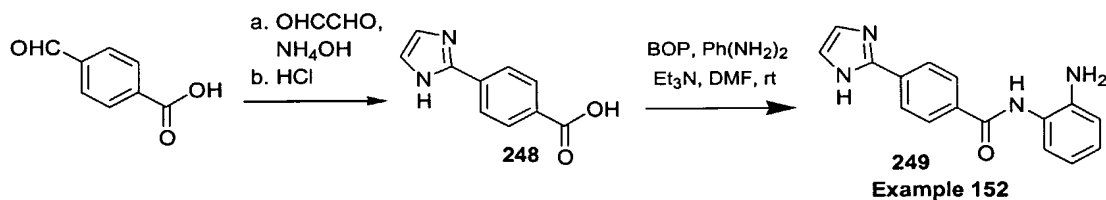
Step 3: 4-(9-Chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzoic acid (**246**)

**[0304]** To a stirred suspension at room temperature of **245** (795 mg, 2.05 mmol) in anhydrous DMF (10 ml) was added a solution of NaOH (409 mg, 10.22 mmol) in anhydrous MeOH (5.1 ml). Then, the reaction mixture was warmed up to 40°C. After 3 days, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 5 in order to get a pale pinky precipitate. After 30 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **246** (679 mg, 1.84 mmol, 90% yield) as a pale pinky solid.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm): AB system ( $\delta_A$  = 7.92,  $\delta_B$  = 7.40,  $J$  = 8.4 Hz, 4H), 7.56 (t,  $J$  = 8.1 Hz, 1H), 7.47 (d,  $J$  = 7.5 Hz, 1H), 7.31 (d,  $J$  = 8.3 Hz, 1H), 5.59 (bs, 2H), 2.95 (s, 3H).

Step 4: *N*-(2-Amino-phenyl)-4-(9-chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzamide (**247**)

**[0305]** The title compound **247** was obtained from **246** in one step following the same procedure as Example 1, steps 5.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm): 9.65 (s, 1H), AB system ( $\delta_A$  = 7.95,  $\delta_B$  = 7.42,  $J$  = 8.1 Hz, 4H), 7.58 (t,  $J$  = 8.1 Hz, 1H), 7.48 (d,  $J$  = 7.5 Hz, 1H), 7.35 (d,  $J$  = 8.3 Hz, 1H), 7.17 (d,  $J$  = 7.5 Hz, 1H), 7.00 (t,  $J$  = 7.3 Hz, 1H), 6.80 (d,  $J$  = 7.5 Hz, 1H), 6.62 (t,  $J$  = 7.3 Hz, 1H), 5.61 (bs, 2H), 4.91 (s, 2H), 2.97 (s, 3H).

**Scheme 41**



**Example 152**

Step 1: 4-(1H-imidazol-2-yl)-benzoic acid (**248**)

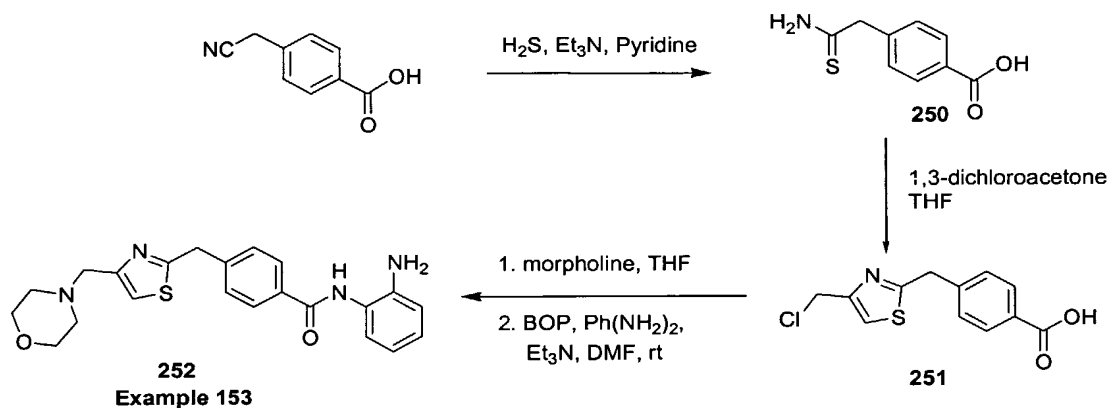
**[0306]** To a stirred solution of 4-formylbenzoic acid (2.00 g, 12.3 mmol) in ammonium hydroxide (9 ml) was added glyoxal (2.86 ml, 20.0 mmol). The reaction mixture was stirred 16 h at room

temperature. 1N HCl was added to the reaction mixture to acidify to pH 5. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **248** (2.08 g, 83%) as a white solid. LRMS: 188.1 (Calc.); 189.1 (found).

Step 2: *N*-(2-Amino-phenyl)-4-(1H-imidazol-2-yl)-benzamide (**249**)

**[0307]** The title compound **249** was obtained following the same procedure as Example 1, step 5.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm):  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 9.72 (bs, 1H), 8.07 (s, 4H), 7.26 (s, 2H), 7.18 (d,  $J = 7.9$  Hz, 1H), 6.98 (dd,  $J = 7.5, 7.5$  Hz, 1H), 6.79 (d,  $J = 7.9$  Hz, 1H), 6.60 (dd,  $J = 7.5, 7.5$  Hz, 1H). MS: (calc.) 278.1; (obt.) 279.1 ( $\text{MH}^+$ ).

**Scheme 42**



Step 1: 4-Thiocarbamoylmethylbenzoic acid (**250**)

**[0308]** To a stirred suspension of 4-cyanomethylbenzoic acid (1.65 g, 10.24 mmol) and  $\text{Et}_3\text{N}$  (5 ml) in pyridine,  $\text{H}_2\text{S}$  was bubbled during 3 h. The reaction mixture was stirred 16 h at room temperature. Water was then added to the reaction mixture which was agitated for 1 h before acidifying to pH 6 with 1M HCl. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **250** (2.08 g, 83%) as a white solid.  $^1\text{H}$  NMR (DMSO)  $\delta$  (ppm): 12.85 (bs, 1H), 9.53 (bs, 1H), 9.43 (bs, 1H), 7.88 (d,  $J = 8.1$  Hz, 2H), 7.44 (d,  $J = 8.1$  Hz, 2H), 3.88 (s, 2H).

Step 2: 4-(4-Chloromethylthiazol-2-ylmethyl)benzoic acid (**251**)

**[0309]** A solution of **250** (729 mg, 3.73 mmol) and 1,3-dichloroacetone (474 mg, 3.73 mmol) in THF (30 ml) was stirred at  $40^\circ\text{C}$  during 48h. The solvent was evaporated then the residue was dissolved in ethyl acetate, washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and

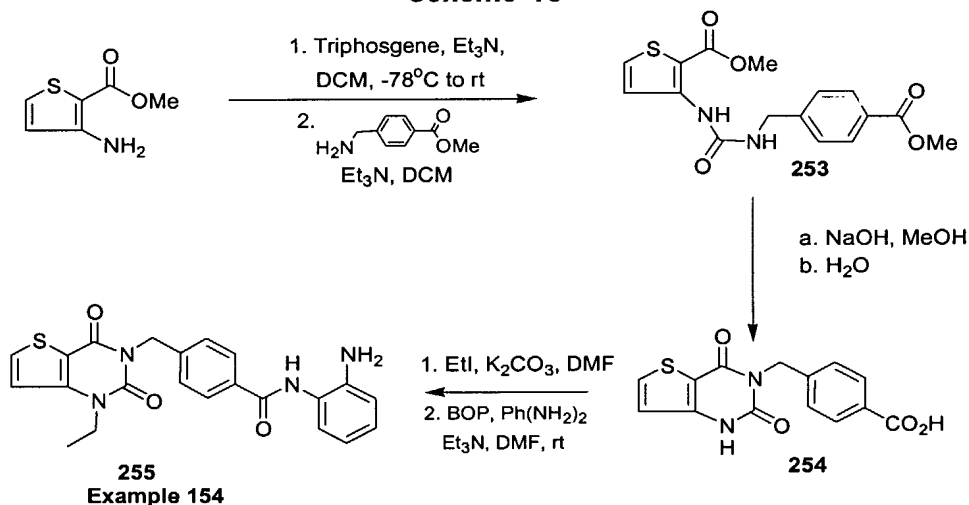
concentrated. The crude residue was purified by flash chromatography on silica gel (2-4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound (827 mg, 83% yield) as a white solid. <sup>1</sup>H NMR (DMSO) δ (ppm): 12.93 (bs, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 4.78 (s, 2H), 4.42 (s, 2H).

Step 3: N-(2-Amino-phenyl)-4-(4-morpholin-4-ylmethyl-thiazol-2-ylmethyl)-benzamide (**252**)

**[0310]** K<sub>2</sub>CO<sub>3</sub> (599 mg, 4.33 mmol) was added to a solution of **251** (527 mg, 1.97 mmol) and morpholine (189 μl, 2.17 mmol) in THF (15 ml) was refluxed during 48h. The solvent was evaporated. The crude residue was purified by flash chromatography on silica gel (3-50% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound **252** (238 mg, 38% yield) as a pale yellow solid. LRMS: 318.2 (calc) 319.2 (found).

**[0311]** The title compound **252** was obtained following the same procedure as Example 1, step 5. <sup>1</sup>H NMR (DMSO) δ (ppm): 9.63 (bs, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.1, 8.1 Hz, 1H), 4.90 (bs, 2H), 4.40 (s, 2H), 3.59-3.56 (m, 6H), 2.44-2.38 (m, 4H). LRMS: 408.2 (calc) 409.2 (found).

**Scheme 43**



**Example 154**

Step 1: Methyl 3-[3-(4-methoxycarbonyl-benzyl)-ureido]-thiophene-2-carboxylate (**253**)

**[0312]** The procedure described by Nakao (K. Nakao, R. Shimizu, H. Kubota, M. Yasuhara, Y. Hashimura, T. Suzuki, T. Fujita and H. Ohmizu; *Bioorg. Med. Chem.* **1998**, 6, 849-868.) was followed

to afford the title compound **253** (1.01 g, 91%) as a yellow solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 9.55 (bs, 1H), 8.00-7.97 (m, 3H), 7.42-7.37 (m, 3H), 5.45 (t,  $J = 5.8$  Hz, 1H), 4.52 (d,  $J = 6.0$  Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H).

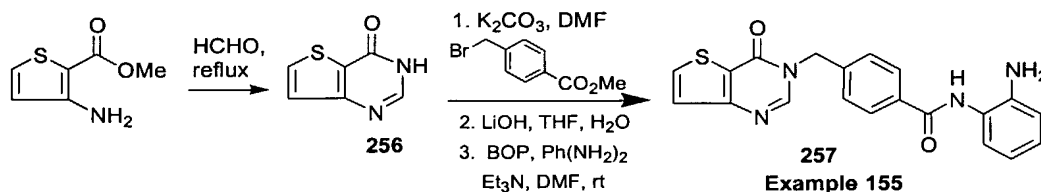
Step 2: 4-(2,4-Dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzoic acid (**254**)

**[0313]** To a suspension of **253** (422 mg, 1.21 mmol) in MeOH (15 ml) was added NaOH (145 mg, 3.63 mmol). The reaction mixture was heated at  $60^\circ\text{C}$  during 16 h. Water (1 ml) was then added and the reaction mixture was stirred for 1 more hour. The solvent was evaporated and the residue was dissolved in water and acidified to pH 5 with HCl 1M. The precipitate was filtered to afford the desired compound **254** (348 mg, 95%) as a white solid. LRMS: 302.0 (Calc.); 303.0 (found).

Steps 3: N-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (**255**)

**[0314]** The title compound **255** was obtained as a yellow solid (73%) following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 5.  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 9.61 (bs, 1H, NH), 8.22 (d,  $J = 5.5$  Hz, 1H, CH), 7.91 (d,  $J = 8.2$  Hz, 2H, CH), 7.43-7.40 (m, 3H, CH), 7.15 (d,  $J = 7.4$  Hz, 1H, CH), 6.96 (dd,  $J = 7.6, 7.6$  Hz, 1H, CH), 6.77 (d,  $J = 7.1$  Hz, 1H, CH), 6.59 (dd,  $J = 7.4, 7.4$  Hz, 1H, CH), 5.17 (s, 2H,  $\text{NCH}_2$ ), 4.88 (bs, 2H,  $\text{NH}_2$ ), 4.09 (q,  $J = 7.0$ , 2H,  $\text{CH}_2$ ), 1.22 (t,  $J = 7.0$ , 3H,  $\text{CH}_3$ ). LRMS: 420.1 (calc.); 421.0 (found).

**Scheme 44**



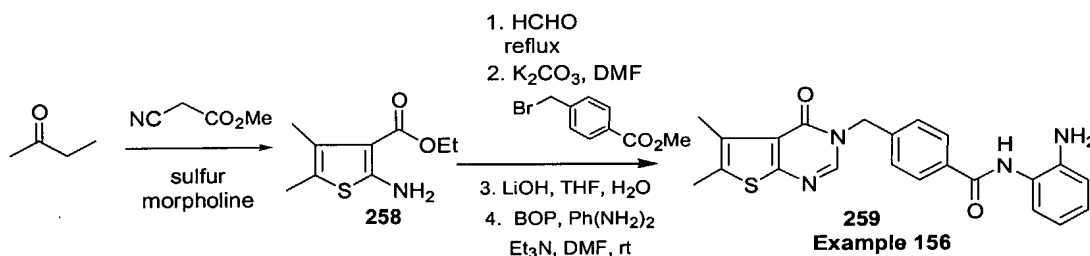
**Example 155**

Step 1: 3H-Thieno[3,2-d]pyrimidin-4-one (**256**)

**[0315]** Methyl-3-amino-2-thiophene carboxylate (510 mg, 3.24 mmol) was dissolved in formamide (20 ml) and heated at  $170^\circ\text{C}$  16h. The solvent was evaporated. The crude residue was then purified by flash chromatography on silica gel (2-4% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford the title compound **256** (157 mg, 32% yield). LRMS: 152.0 (Calc.); 152.9 (found).

Step 2: *N*-(2-Aminophenyl)-4-(4-oxo-4*H*-thieno[3,2-*d*]pyrimidin-3-ylmethyl)-benzamide (**257**)

**[0316]** Following the procedure described in Example 85, step 1 but substituting the previous compound for **119**, followed by Example 1, step 4, 5, the title compound **257** was obtained in 41% yield. <sup>1</sup>H NMR: (DMSO)  $\delta$  (ppm): 9.61 (bs, 1H), 8.70 (s, 1H), 8.22 (dd,  $J = 5.2, 0.5$  Hz, 1H), 7.95 (d,  $J = 8.2$  Hz, 2H), 7.47 (d,  $J = 8.5$  Hz, 2H), 7.44 (dd,  $J = 5.2, 0.6$  Hz, 1H), 7.15 (d,  $J = 7.7$  Hz, 1H), 6.96 (dd,  $J = 6.9, 6.9$  Hz, 1H), 6.77 (d,  $J = 7.1$  Hz, 1H), 6.58 (dd,  $J = 7.0, 7.0$  Hz, 1H), 5.31 (s, 2H), 4.87 (bs, 2H). MS: 376.1 (calc.); 377.1 (found).

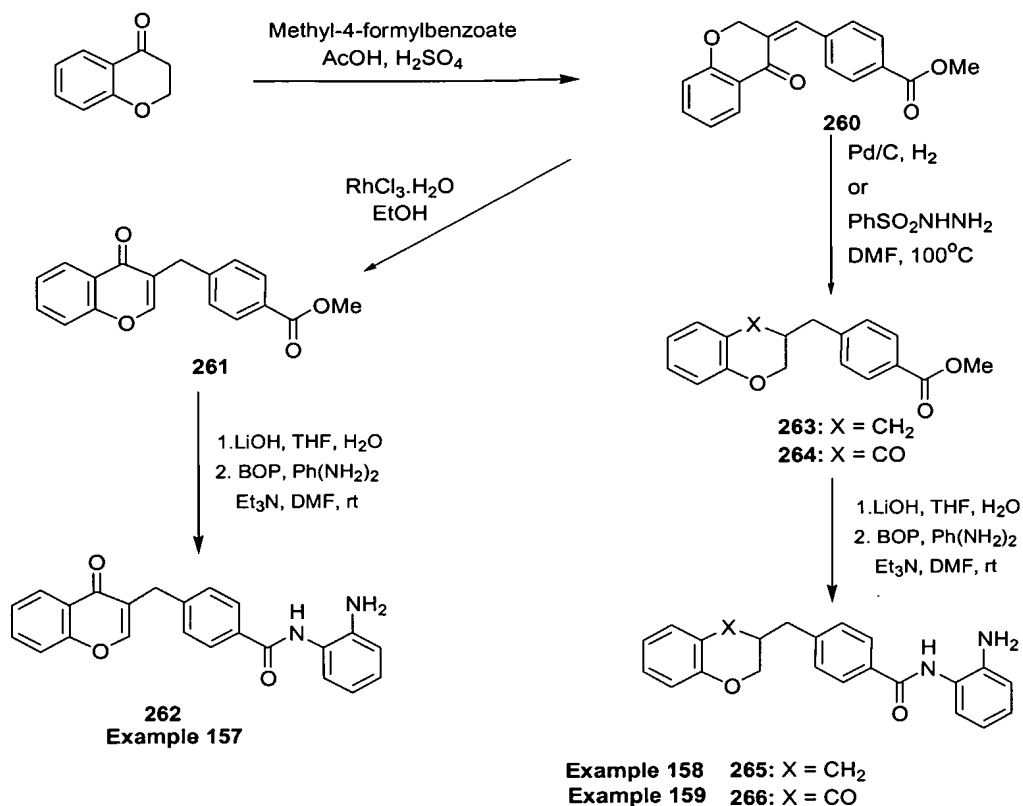
**Scheme 45****Example 156**Step 1: Methyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (**258**)

**[0317]** The procedure described by Hozien (Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab and S. A. Ahmed; *Synht. Commun.* **1996**, 26(20), 3733-3755.) was followed to afford the title compound **258** (1.44 g, 17%) as a yellow solid. LRMS: 197.1 (Calc.); 200.1 (found).

Steps 2: *N*-(2-Amino-phenyl)-4-(5,6-dimethyl-4-oxo-4*H*-thieno[2,3-*d*]pyrimidin-3-ylmethyl)-benzamide (**259**)

**[0318]** Following the procedure described in Example 155, step 1, 2 but substituting **258** for **256**, the title compound **259** was obtained as a white solid (55%). <sup>1</sup>H NMR: (DMSO)  $\delta$  (ppm): 9.61 (bs, 1H), 8.57 (s, 1H), 7.94 (d,  $J = 8.0$  Hz, 2H), 7.45 (d,  $J = 7.7$  Hz, 2H), 7.16 (d,  $J = 7.7$  Hz, 1H), 6.96 (dd,  $J = 7.6, 7.6$  Hz, 1H), 6.77 (d,  $J = 8.0$  Hz, 1H), 6.59 (dd,  $J = 7.4, 7.4$  Hz, 1H), 5.25 (s, 2H), 4.87 (bs, 2H), 2.39 (s, 3H), 2.37 (s, 3H). LRMS: 404.1 (calc); 405.0 (found).

**Scheme 46**



**Example 157**

Step 1: Methyl 4-(4-oxo-chroman-3-ylidenemethyl)-benzoate (**260**)

**[0319]** Concentrated H<sub>2</sub>SO<sub>4</sub> (2 ml) was slowly added to a solution of 4-chromanone (2.00 g, 13.50 mmol) and methyl-4-formylbenzoate (2.11 g, 12.86 mmol) in glacial acetic acid. The reaction mixture was stirred 16 h at room temperature. The solvent was concentrated to half volume the resulting precipitate was filtered and rinsed with ethyl acetate to afford the title compound **260** (3.11 g, 82%) as a purple solid. <sup>1</sup>H NMR: (DMSO) δ (ppm): 8.05 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.64-7.59(m, 3H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H), 3.89 (s, 3H).

Step 2: Methyl-4-(4-oxo-4H-chromen-3-ylmethyl)-benzoate (**261**)

**[0320]** Water (0.2 ml) and RhCl<sub>3</sub>.H<sub>2</sub>O (7 mg, 0.034 mmol) was added to a suspension of compound **260** (200 mg, 0.680 mmol) in EtOH (2 ml) and CHCl<sub>3</sub> (2 ml). The reaction mixture was stirred 16 h at 70°C. The reaction mixture was cooled down and diluted in ethyl acetate, washed with

brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (0.5-1%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to afford the title compound **261** (118 mg, 59%) as a white solid.  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 8.45 (s, 1H), 8.03 (dd,  $J = 7.9, 1.8$  Hz, 1H), 7.87 (d,  $J = 8.4$  Hz, 2H), 7.83-7.77 (m, 1H), 7.65 (d,  $J = 8.3$  Hz, 1H), 7.50-7.43 (m, 3H), 3.82 (s, 3H), 3.80 (s, 2H).

Step 3: *N*-(2-Amino-phenyl)-4-(4-oxo-4H-chromen-3-ylmethyl)-benzamide (**262**)

**[0321]** The title compound **262** was obtained following the same procedure as Example 1, step 4, 5.  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 9.56 (bs, 1H), 8.45 (s, 1H), 8.04 (d,  $J = 7.9$  Hz, 1H), 7.88 (d,  $J = 8.4$  Hz, 2H), 7.80 (dd,  $J = 7.5, 7.5$  Hz, 1H), 7.65 (d,  $J = 8.4$  Hz, 1H), 7.51-7.42 (m, 3H), 7.14 (d,  $J = 7.9$  Hz, 1H), 6.96 (dd,  $J = 7.3, 7.3$  Hz, 1H), 6.76 (d,  $J = 7.9$  Hz, 1H), 6.58 (dd,  $J = 7.3, 7.3$  Hz, 1H), 4.86 (bs, 2H), 3.80 (s, 2H). LRMS: 370.1 (calc.); 371.1 (found).

**Example 158**

Step 2: Methyl 4-chroman-3-ylmethyl-benzoate (**263**)

**[0322]** Pd/C 10% was added to a suspension of **260** (200 mg, 0.68 mmol) in MeOH (40 ml) and DMA (10 ml) which was previously purged under vacuum. The reaction mixture was stirred during 4 h at room temperature. After evaporation of the MeOH, water was added to the oily residue and the precipitate obtained was filtered. The crude residue was then purified by flash chromatography on silica gel (5-8% AcOEt/Hex) to afford the title compound **263** (114 mg, 59%) as a white solid. LRMS: 282.1 (Calc.); 283.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-chroman-3-ylmethyl-benzamide (**265**)

**[0323]** The title compound **265** was obtained following the same procedure as Example 1, steps 4 and 5.  $^1\text{H}$  NMR: (acetone)  $\delta$  (ppm): 9.06 (bs, 1H), 8.01 (d,  $J = 7.9$  Hz, 2H), 7.42 (d,  $J = 8.4$  Hz, 2H), 7.31 (d,  $J = 7.9$  Hz, 1H), 7.08-6.98 (m, 3H), 6.87 (d,  $J = 7.5$  Hz, 1H), 6.82-6.66 (m, 3H), 4.62 (s, 2H), 4.22-4.17 (m, 1H), 4.88-3.81 (m, 1H), 2.88-2.71 (m, 3H), 2.61-2.53 (m, 1H), 2.41-2.33 (m, 1H). LRMS: 358.2 (calc.); 359.1 (found).

**Example 159**

Step 2: Methyl 4-(4-oxo-chroman-3-ylmethyl)-benzoate (**264**)

**[0324]** A suspension of **260** (400 mg, 1.36 mmol) and benzenesulfonyl hydrazine (702 mg, 4.08 mmol) in DMF (7 ml) was stirred at 100°C during 48h. The solvent was evaporated and the

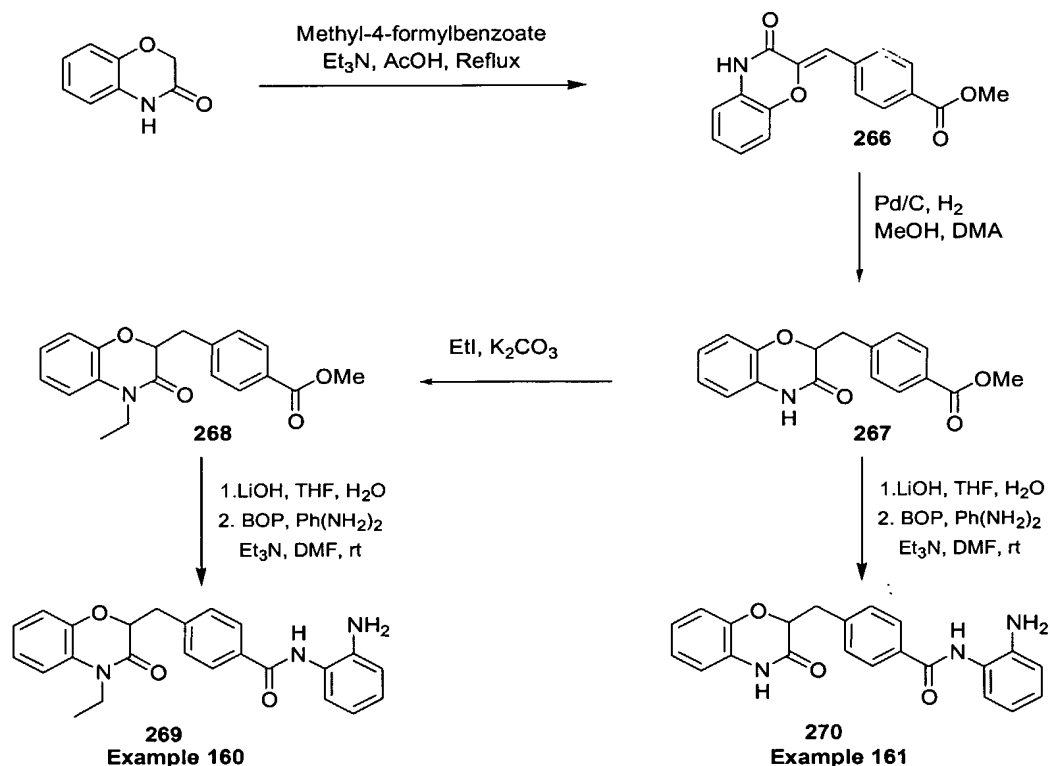


residue was diluted in AcOEt, washed with  $\text{NH}_4\text{Cl}$  sat., brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5% AcOEt/HEx) to afford the title compound **264** (170 mg, 42%) as a white solid. LRMS: 296.1 (Calc.); 297.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(4-oxo-chroman-3-ylmethyl)-benzamide (**266**)

**[0325]** The title compound **266** was obtained following the same procedure as Example 1, steps 4 and 5.  $^1\text{H}$  NMR: (acetone)  $\delta$  (ppm): 9.62 (bs, 1H), 7.93 (d,  $J = 7.9$  Hz, 2H), 7.79 (d,  $J = 7.9$  Hz, 1H), 7.58 (dd,  $J = 7.0, 7.0$  Hz, 1H), 7.39 (d,  $J = 7.9$  Hz, 2H), 7.17-7.04 (m, 3H), 6.97 (dd,  $J = 7.0, 7.0$  Hz, 1H), 6.78 (d,  $J = 7.9$  Hz, 1H), 6.60 (dd,  $J = 7.5, 7.5$  Hz, 1H), 4.88 (s, 2H), 4.44-4.39 (m, 1H), 4.28-4.21 (m, 1H), 2.26-3.21 (m, 2H), 2.83-2.74 (m, 1H). LRMS: 372.1 (calc.); 372.1 (found).

**Scheme 47**



**Example 160**

Step 1: Methyl 4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzoate (**266**)

**[0326]** Et<sub>3</sub>N (3.18 ml, 22.8 mmol) was added to a stirring solution of 2-*H*-1,4-benzoxazin-3-(4*H*)one (2.50 g, 16.8 mmol) and methyl 4-formylbenzoate (4.59 g, 27.5 mmol) in Ac<sub>2</sub>O (20 ml). The reaction mixture was refluxed 16h. After this mixture was cooled for 3 days, the solid was filtered and rinsed with ethyl acetate to afford the title compound **266** (657 mg, 13%) as a yellow solid. LRMS: 295.1 (Calc.); 296.0 (found).

Step 2: Methyl 4-(3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl)-benzoate (**267**)

**[0327]** The title compound **267** was obtained following the same procedure as Example 158, step 2. LRMS: 297.1 (Calc.); 298.1 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (**269**)

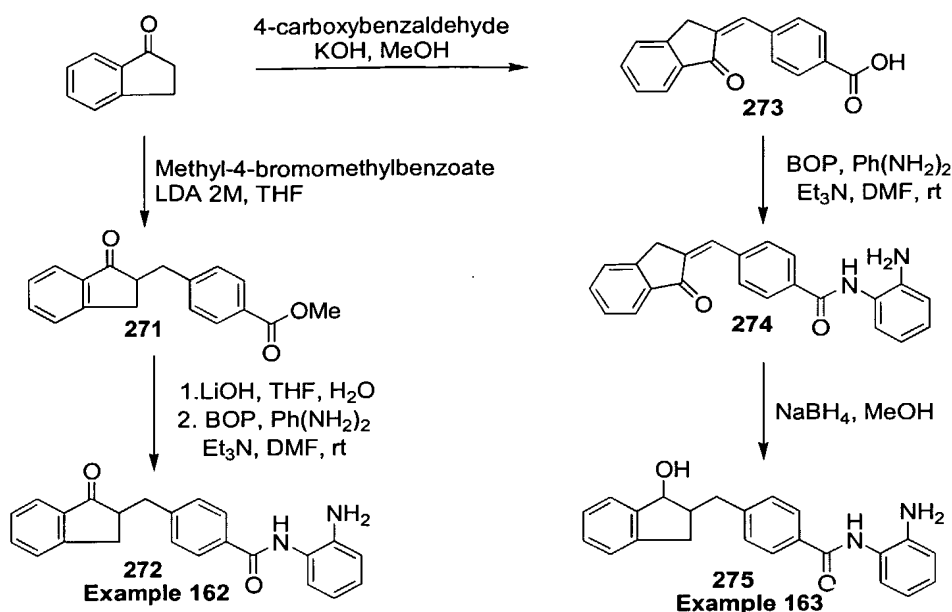
**[0328]** The title compound **269** was obtained from **267** following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 4, 5. <sup>1</sup>H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.11-6.91 (m, 4H), 6.77 (d, J = 7.0 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.95-4.91 (m, 1H), 4.89 (bs, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.28-3.22 (m, 1H), 3.17-2.89 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H). LRMS: 401.2 (calc.); 402.1 (obt.).

**Example 161**

Step 1: *N*-(2-Amino-phenyl)-4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (**270**)

**[0329]** The title compound **270** was obtained from **267** following the same procedure as Example 1, step 4, 5. <sup>1</sup>H NMR: (DMSO) δ (ppm): 10.74 (bs, 1H), 9.61 (bs, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.99-6.85 (m, 5H), 6.78 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.92-4.89 (m, 3H), 3.29-3.23 (m, 1H), 3.15-3.07 (m, 1H). MS: (calc.) 373.1; (obt.) 374.1 (MH)<sup>+</sup>.

## Scheme 48



## Example 162

Step 1: Methyl 4-(1-oxo-indan-2-ylmethyl)-benzoate (**271**)

**[0330]** A 2M LDA solution in THF (4.16 ml, 8.32 mmol) was added to a solution of indanone (1.00 g, 7.57 mmol) in THF (10 ml) at  $-60^\circ\text{C}$ . The solution was slowly warmed to  $0^\circ\text{C}$  during a period of 15 min. and was agitated for 15 more min. The reaction was then cooled to  $-78^\circ\text{C}$  and a solution of methyl-4-bromobenzoate (1.73 g, 7.57 mmol) was slowly added. The solution was slowly warmed to  $-20^\circ\text{C}$  and stirred during 4 hours. The reaction mixture was quenched with HCL 1M and the solvent was evaporated. The residue was diluted in ethyl acetate, washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5-20%  $\text{AcOEt}/\text{HEx}$ ) to afford the title compound **271** (245 mg, 17%) as a white solid. LRMS: 280.1 (Calc.); 281.1 (found).

Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylmethyl)-benzamide (**272**)

**[0331]** The title compound **272** was obtained following the same procedure as Example 1, step 4, 5.  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 9.59 (bs, 1H), 7.91 (d,  $J = 7.6$  Hz, 2H), 7.69-7.64 (m, 2H), 7.54 (d,  $J = 7.6$  Hz, 1H), 7.45-7.40 (m, 3H), 7.16 (d,  $J = 8.2$  Hz, 1H), 6.96 (dd,  $J = 7.3, 7.3$  Hz, 1H), 6.77 (d,  $J = 8.2$  Hz, 1H), 6.59 (dd,  $J = 7.3, 7.3$  Hz, 1H), 4.87 (bs, 2H), 3.23-3.14 (m, 3H), 2.85-2.81 (m, 2H). LRMS: 356.1 (calc.); 357.2 (found).

**Example 163**Step 1: 4-(1-Oxo-indan-2-ylidenemethyl)-benzoic acid (**273**)

**[0332]** To a suspension of indanone (2.00 g, 15.1 mmol) and 4-carboxybenzaldehyde (1.89g, 12.6 mmol) in EtOH (10 ml) was added KOH (1.77 g, 31.5 mmol) at 0°C. The reaction mixture was stirred 30 min at 0°C then at room temperature for 16 h. The solvent was evaporated and the residue was dissolved in water, acidified to pH 5 with HCl 1 M. The precipitate was filtered and rinsed with water to afford the title compound **273** (2.27 g, 57%) as a yellow solid. LRMS: 264.1 (Calc.); 265.0 (found).

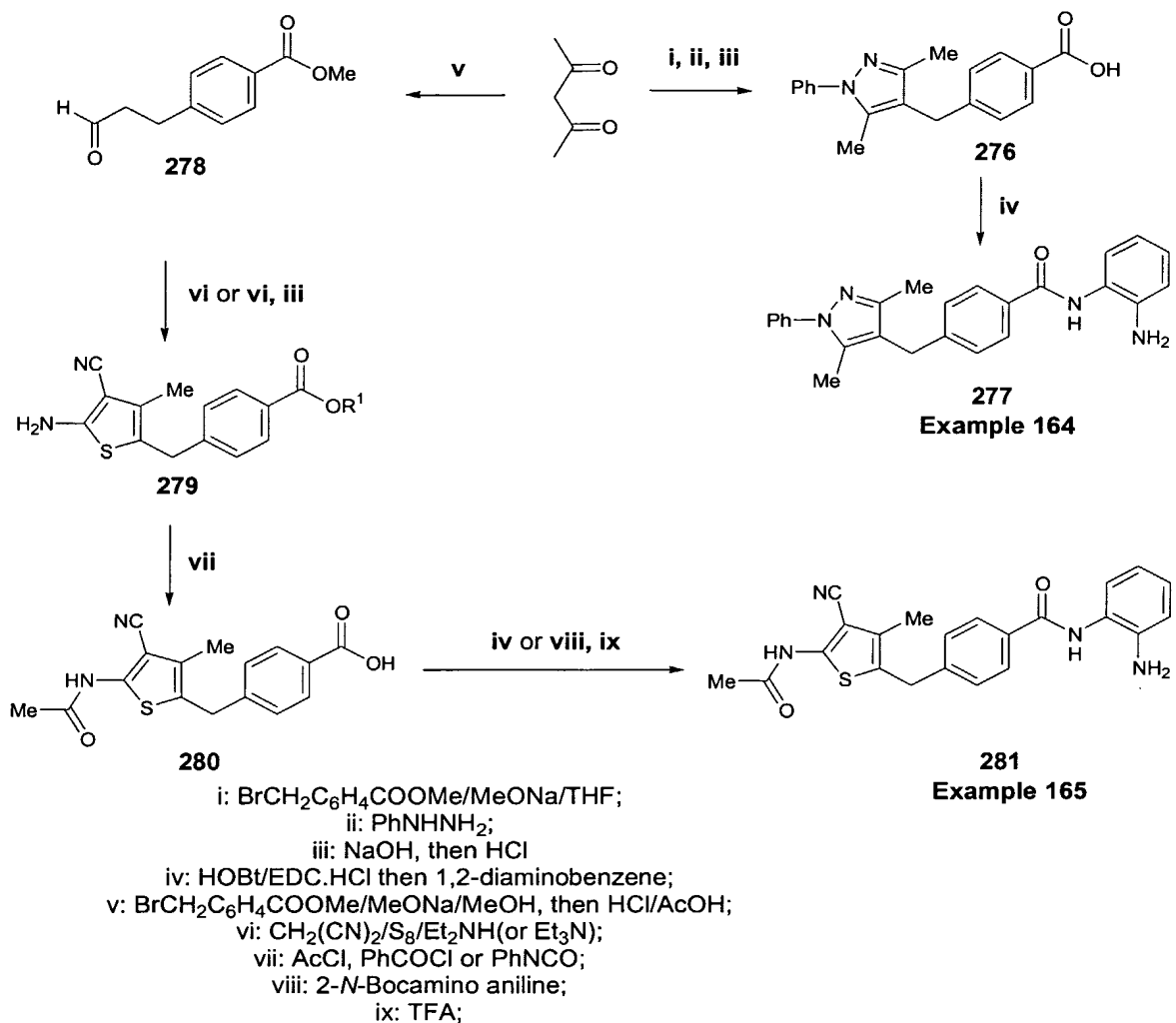
Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylidenemethyl)-benzamide (**274**)

**[0333]** The title compound **274** was obtained following the same procedure as Example 1, step 5. LRMS: 354.1 (Calc.); 355.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(1-hydroxy-indan-2-ylmethyl)-benzamide (**275**)

**[0334]** To a suspension of **274** (300 mg, 0.85 mmol) in MeOH (8 ml) and water (1 ml) was added NaBH<sub>4</sub> (75 mg, 1.95 mmol). The reaction mixture was stirred at 50°C 16h and cooled down. Water was added to the solution and the precipitated was filtered and rinsed with cold water to afford the title compound **275** (224 mg, 74%) as a white solid. <sup>1</sup>H NMR: (acetone) δ (ppm): 9.05 (bs, 1H), 8.00 (dd, J = 8.2, 2.7 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.38-7.30 (m, 2H), 7.22-7.12 (m, 3H), 7.01 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.87 (dd, J = 8.0, 1.1 Hz, 1H), 6.68 (dd, J = 7.6, 7.6 Hz, 1H), 4.98 (t, J = 5.8 Hz, 0.4H), 4.89 (t, J = 6.7 Hz, 0.6H), 4.63 (bs, 2H), 4.45 (d, J = 6.9 Hz, 0.6H), 4.06 (d, J = 6.0 Hz, 0.4H), 3.30-3.19 (m, 1H), 2.88-2.48 (m, 3H, CH<sub>2</sub>). LRMS: 358.2 (calc.); 359.1 (found).

Scheme 49

**Example 164**Step 1: 4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-benzoic acid (276)

**[0335]** To a solution of NaH (60% in mineral oil, 250 mg, 6.3 mmol) at 0°C acetyl acetone (0.646 ml, 6.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester **2** (1.2 g, 5.2 mmol). The reaction mixture stirred 1 hour at room temperature and refluxed for 2 hours. Phenyl hydrazine (0.51 ml, 5.2 mmol) was added and the reaction mixture refluxed for an additional hour. THF was removed in vacuum and the oily residue was partitioned between water and ethyl acetate. Organic layer was separated, dried, evaporated and purify by chromatography on a silica gel column, eluent EtOAc – hexane (1:1) to produce an oily material (800mg) which was treated with a solution of

NaOH (0.8 g, 20 mmol) in 20 ml water for 1 hour at room temperature. The following steps, - acidification with HCl (pH 6), extraction of the resultant emulsion with ethyl acetate, drying the extract with sodium sulfate, evaporation and column chromatography (eluent EtOAc – hexane, 1:1) afforded 390 mg of a mixture of **276** (the title compound) and **278** (molar ratio 1:2). [M-1]<sup>+</sup> 307.0 and 191.1. This mixture was taken for the next step as is.

Step 2. *N*-(2-Amino-phenyl)-4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-benzamide (**277**)

**[0336]** Following a procedure analogous to that described in Example 92, step 2, but substituting **276** for **143**, the title compound **277** was obtained in 25% yield (purified by chromatography using as eluent EtOAc - hexane, 1:1). <sup>1</sup>H NMR: (300 MHz, DMSO-d<sub>6</sub>, δ (ppm): 9.64 (s, 1H); 7.97 (d, J = 7.6 Hz, 2H), 7.42-7.56 (m, 5H), 7.37 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 4.93 (s, 2H), 3.92 (s, 2H), 2.34 (s, 3H), 2.18 (s, 3H).

### Example 165

Step 1: 4-(3-Oxo-butyl)-benzoic acid (**278**)

**[0337]** To a solution of acetyl acetone (5.0 ml, 49 mmol) at room temperature NaOMe (25% wt, 10.8 ml, 47.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester **2** (9.0 g, 39.3 mmol). The reaction mixture refluxed 3 hours, cooled to the room temperature and acidified with HCl (pH 1-2). Evaporation of the resultant solution yielded a residue, which was refluxed in a mixture of glacial AcOH (50 ml) and conc. HCl (25 ml) for 4 hours. Acids were removed in vacuum and the residue was triturated with water to form a crystalline material, which was collected by filtration and dried to afford **278** (6.72 g, 80% yield). [M-1] 191.1.

Step 2. 4-(5-Amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid **279**

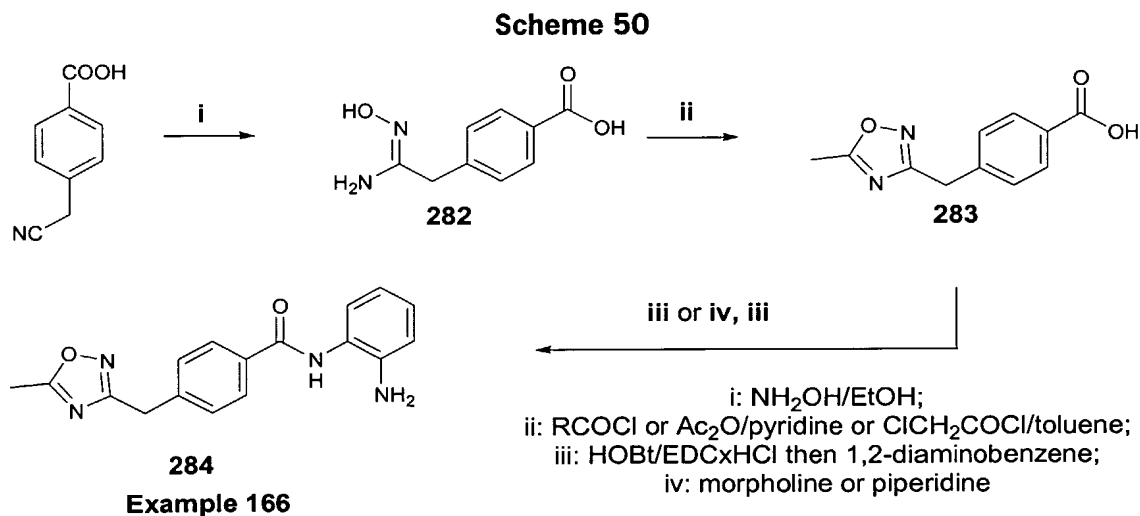
**[0338]** To a refluxing suspension of 4-(3-oxo-butyl)-benzoic acid **278** (700 mg, 3.65 mmol), malonodinitrile (241 mg, 3.65 mmol) and sulfur (130 mg, 3.65 mmol) in 20 ml EtOH, diethylamine (0.5 ml, 4.8 mmol) was added. The reaction mixture refluxed 1 hour, cooled to the room temperature, acidified with conc. HCl (pH 4-5) and evaporated to yield a solid residue. This material was partitioned between water and ethyl acetate, organic layer was separated, dried, evaporated and chromatographed on a silica gel column, eluent EtOAc-hexane, 1:1, to afford the title compound **279** (300 mg, 30% yield). <sup>1</sup>H NMR: (300 MHz, DMSO-d<sub>6</sub>, δ ppm): 7.87 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.98 (s, 2H), 3.92 (s, 2H), 2.03 (s, 3H).

Step 3. 4-(5-Acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid **280**

**[0339]** To a solution of 4-(5-amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid **279** (230 mg, 0.86 mmol) in a solvent mixture acetone (5 ml) – dichloromethane (5 ml) at room temperature acetyl chloride (0.305 ml, 4.3 mmol) was added. After 2 hours of stirring at the same conditions a precipitate of the title compound **280** formed which was collected and dried (200 mg, 75% yield). [M-1] 313.1.

Step 4: N-(2-Amino-phenyl)-4-(5-acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)- benzamide (**281**)

**[0340]** Following a procedure analogous to that described in Example 92, step 2, but substituting **280** for **143**, the title compound **281** was obtained in 25% yield. <sup>1</sup>H NMR (DMSO)  $\delta$  (ppm): 9.61 (s, 1H); 7.91 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 6.6 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.10 (s, 2H), 2.19 (s, 3H), 2.16 (s, 3H). [M+1] 405.0.

**Example 166**Step 1. 4-(N-Hydroxycarbamimidoylmethyl)-benzoic acid (**282**)

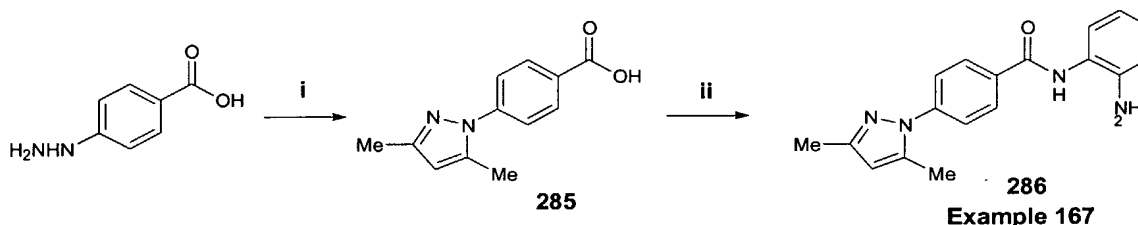
**[0341]** A suspension of 4-cyanomethyl benzoic acid (2.07 g, 12.86 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (1.79 g, 25.71 mmol) and potassium hydroxide (2.16 g, 38.57 mmol) in 70 ml ethanol refluxed for 36 hours, poured into 100 ml water and acidified with conc. HCl (pH 5-6). EtOH was removed in vacuum and the remaining suspension was treated with another 100 ml water. A precipitate formed which was collected and dried to afford the title compound **282**. [M+1]195.1.

Step 2. 4-(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzoic acid (**283**)

**[0342]** A solution of 4-(N-hydroxycarbamimidoylmethyl)-benzoic acid **282** (388 mg, 2.0 mmol) in pyridine (8 ml) was treated with acetic anhydride (0.283 ml, 3.0 mmol). The resultant solution refluxed 6 hours, evaporated in vacuum and the remaining solid was triturated with water, collected by filtration, dried and purified by chromatography on a silica gel column, eluent EtOAc, EtOAc-MeOH (10:1) and finally EtOAc-MeOH (1:1), to produce **283** (164 mg, 38% yield).  $[M-1]^-$  217.1

Step 3. N-(2-Amino-phenyl)-4-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide (**284**)

**[0343]** For the preparation of the title compound **284**, a procedure analogous to that described in Example 92, step 2, but substituting **283** for **143**, the title compound **284** was obtained.  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm): 9.62 (s, 1H), 7.93 (d,  $J = 7.9$  Hz, 2H), 7.42 (d,  $J = 8.4$  Hz, 1H), 7.16 (d,  $J = 7.5$  Hz, 1H), 6.97 (t,  $J = 7.9$  Hz, 1H), 6.78 (d,  $J = 7.5$  Hz, 1H), 6.60 (t,  $J = 7.9$  Hz, 1H), 4.92 (s, 2H), 4.14 (s, 2H), 2.55 (s, 3H).  $[M+1]^+$  309.2

**Scheme 51**

i: Acetyl acetone/EtOH;  
ii: HOBt/EDC·HCl then 1,2-diaminobenzene;

**Example 167**Step 1: 4-(3,5-Dimethyl-pyrazol-1-yl)-benzoic acid (**285**)

**[0344]** A solution of 4-hydrazino-benzoic acid (0.60 g, 3.95 mmol) and acetyl acetone (0.405 ml, 3.95 mmol) in ethanol (20 ml) refluxed for 1 hour. Ethanol was removed in vacuum and the remaining solid was triturated with water and collected by filtration to produce **285** (0.71 mg, 83% yield).  $[M-1]^-$  215.1.

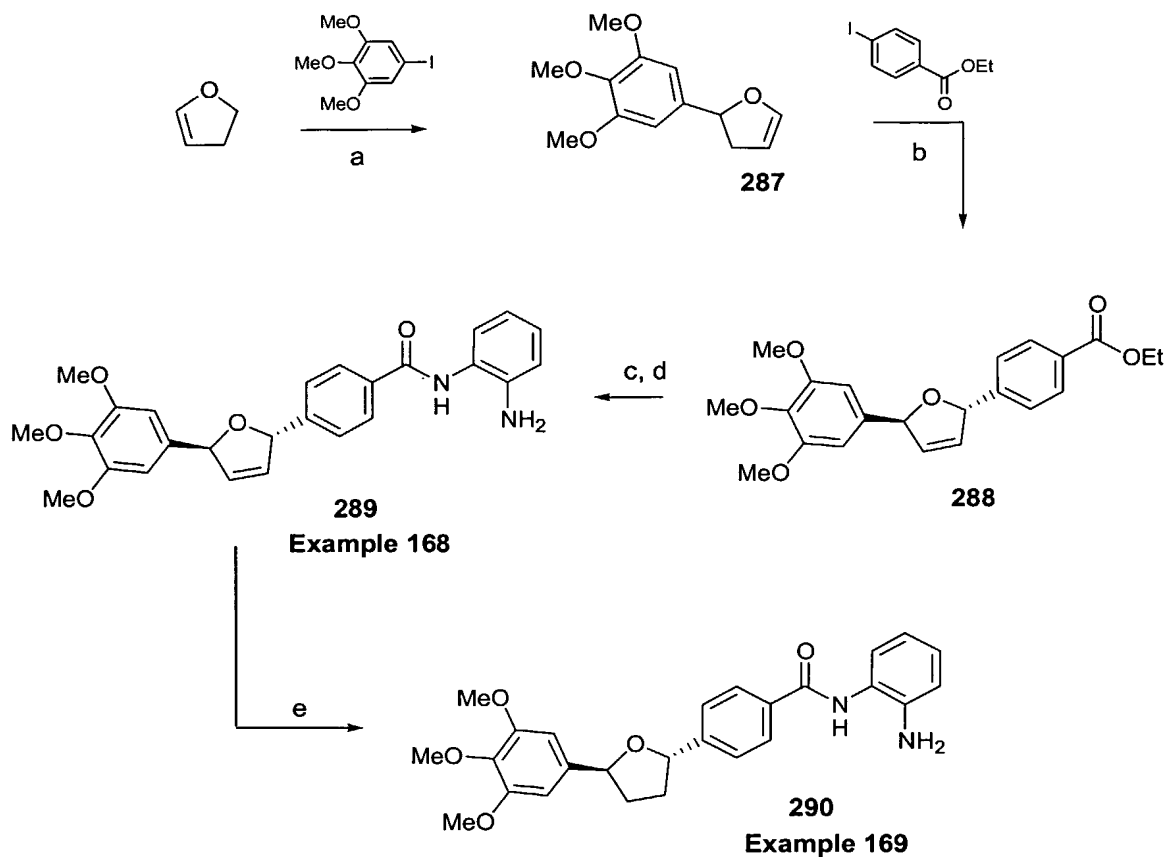
Step 2. N-(2-Amino-phenyl)-4-(3,5-dimethyl-pyrazol-1-yl)-benzamide (**286**)

**[0345]** For the preparation of the title compound **286**, a procedure analogous to that described in Example 92, step 2, but substituting **285** for **143**, the title compound **286** was obtained in 34% yield (purified by chromatography using as eluent  $\text{CH}_2\text{Cl}_2$ -methanol, 19:1).  $^1\text{H}$  NMR: (DMSO)  $\delta$  (ppm):



9.73 (s, 1H); 8.09 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 4.92 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H).  $[M+1]^+$  303.3

### Scheme 52



- a. 2.5% Pd(OAc)<sub>2</sub> / nBu<sub>4</sub>NCl (1 eq) / KOAc (3 eq) / 2.5% PPh<sub>3</sub> / DMF / 80°C
- b. 3-4% Pd(OAc)<sub>2</sub> / 9% PPh<sub>3</sub> / Ag<sub>2</sub>CO<sub>3</sub> (2 eq) / CH<sub>3</sub>CN / 80°C
- c. LiOH · H<sub>2</sub>O / THF-H<sub>2</sub>O (2:1)
- d. 1,2-phenylenediamine / BOP / Et<sub>3</sub>N / DMF
- e. PtO<sub>2</sub> / H<sub>2</sub> (1 atm) / AcOEt

### Example 168

#### Step 1: 2-(3,4,5-Trimethoxy-phenyl)-2,3-dihydro-furan (**287**)

**[0346]** To a solution of 5-iodo-1,2,3-trimethoxybenzene (900 mg, 3.06 mmol) and 2,3-dihydrofuran (1.16 mL, 15.3 mmol) in dry DMF (8 mL) were added PPh<sub>3</sub> (20 mg, 0.077 mmol), KOAc

(901 mg, 9.18 mmol), *n*-Bu<sub>4</sub>NI (850 mg, 3.06 mmol) and Pd(OAc)<sub>2</sub> (17 mg, 0.077 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was diluted with AcOEt and water. After separation, the organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 20/80) to afford the title compound **287** (311 mg, 1.32 mmol, 43% yield). <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.59 (s, 2H), 6.45 (m, 1H), 5.45 (dd, *J* = 10.5, 8.4 Hz, 1H), 4.97 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.06 (m, 1H), 2.62 (m, 1H).

Step 2: 4-[5-(3,4,5-Trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzoic acid ethyl ester (**288**)

**[0347]** To a solution of **287** (200 mg, 0.846 mmol) and 4-Iodo-benzoic acid ethyl ester (468 mg, 1.69 mmol) in dry acetonitrile (4 mL) were added PPh<sub>3</sub> (20 mg, 0.076 mmol), Ag<sub>2</sub>CO<sub>3</sub> (467 mg, 1.69 mmol) and Pd(OAc)<sub>2</sub> (7 mg, 0.03 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was filtered through celite and washed with AcOEt. Water was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 30/70) to afford the title compound **288** (280 mg, 0.728 mmol, 86% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.05 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 6.61 (s, 2H), 6.18-5.95 (m, 4H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 1.39 (t, *J* = 7.0 Hz).

Step 3: *N*-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide (**289**)

**[0348]** Following a procedure analogous to that described in Example 1, step 4, 5, but substituting **288** for **6**, the title compound **289** was obtained in 48% yield. <sup>1</sup>H NMR (DMSO) δ (ppm): 8.00 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.92-6.82 (m, 2H), 6.61 (s, 2H), 6.14-5.99 (m, 4H), 3.89 (s, 6H), 3.84 (s, 3H).

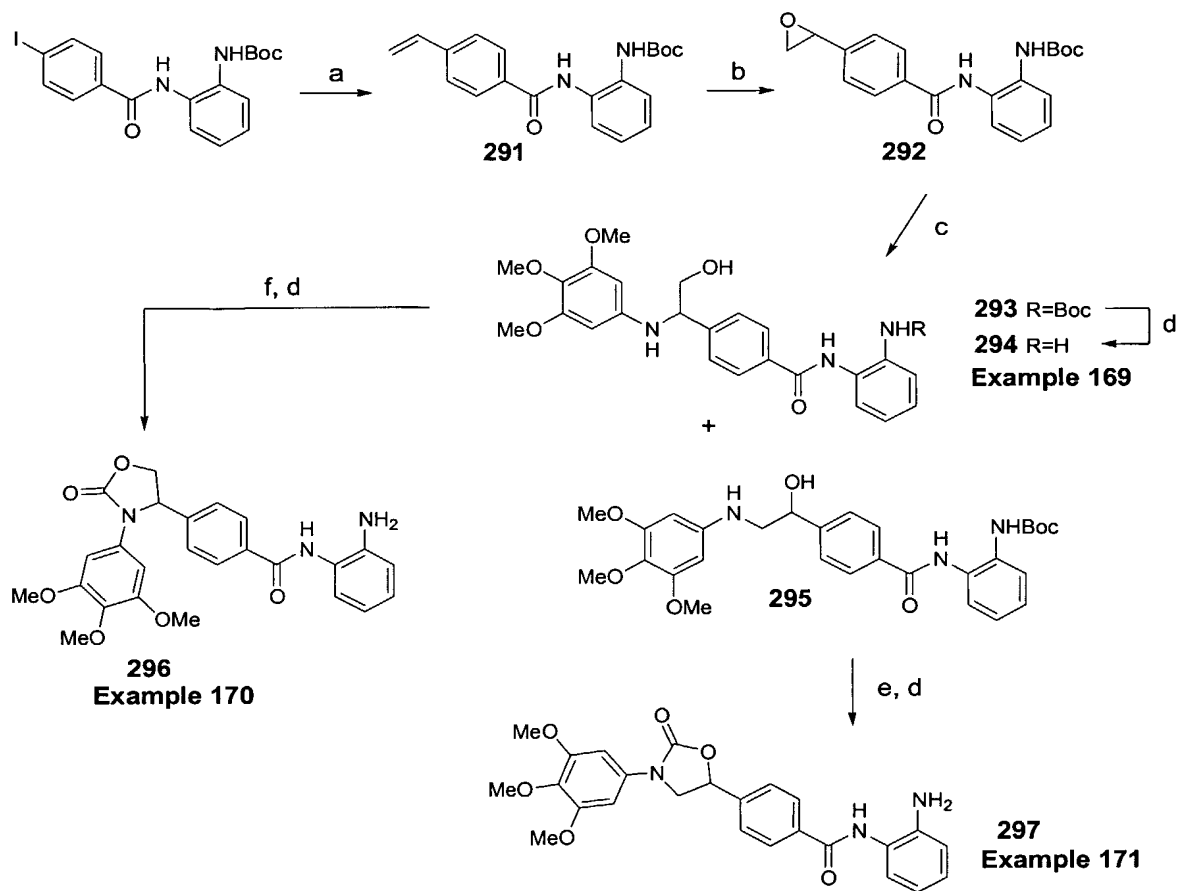
**Example 169**

Step 1: *N*-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzamide. (**290**)

**[0349]** To a degazed solution of **289** (43 mg, 0.096 mmol) in AcOEt (4 mL) was added PtO<sub>2</sub> (3 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature under a 1 atm pressure of H<sub>2</sub> for 16 h. The reaction flask was purged with N<sub>2</sub> then the reaction mixture was filtered through celite, rinsed with MeOH and concentrated. The crude residue was purified three times by flash chromatography on silica gel (MeOH/DCM: 2/98, AcOEt/DCM: 30/70 and AcOEt/CHCl<sub>3</sub>: 30/70) to afford the title compound **290** (10 mg, 0.22 mmol, 23% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.10 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz,

1H), 6.96-6.85 (m, 2H), 6.64 (s, 2H), 5.33 (t, J = 7.0 Hz, 1H), 5.21 (t, J = 7.0 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 2.59-2.40 (m, 2H), 2.09-1.88 (m, 2H).

## Scheme 53



- a. Tributyl(vinyl)tin / Pd(PPh<sub>3</sub>)<sub>4</sub> / Toluene / 100°C
- b. *m*-CPBA / CHCl<sub>3</sub> / r.t.
- c. 3,4,5-trimethoxyaniline / CoCl<sub>2</sub> / CH<sub>3</sub>CN
- d. TFA / DCM
- e. 1,1'-carbonyldiimidazole / DCM / r.t.
- f. 1,1'-carbonyldiimidazole / Et<sub>3</sub>N / Toluene / THF / 90°C

**Example 169**Step 1: [2-(4-Vinyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (**291**)

**[0350]** Following a procedure analogous to that described in Example 143, step 2, but substituting **184** for **221**, the title compound **291** was obtained in 90% yield as a dark yellow oil. <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.18 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.30-7.10 (m, 3H), 6.89 (s, 1H), 6.77 (dd, J = 17.4, 11.0 Hz, 1H), 5.87 (d, J = 17.4 Hz, 1H), 5.39 (d, J = 11.0 Hz, 1H), 1.52 (s, 9H).

Step 2: [2-(4-Oxiranyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (**292**)

**[0351]** To a solution of **291** (4.1 g, 12.1 mmol) in dry CHCl<sub>3</sub> (60 mL) was added *m*-CPBA 70% (3.6 g, 14.5 mmol). The reaction mixture was stirred at room temperature for 5 h then additional *m*-CPBA (0.6 g, 2.4 mmol) was added and the stirring continued for 1 h. A further amount of *m*-CPBA (0.6 g, 2.4 mmol) was added and the reaction mixture was stirred for 16 h. Chloroform and a 10% solution of NaHCO<sub>3</sub> were added and the phases were separated. The organic layer was washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 1/3) to afford the title compound **292** (2.86 g, 8.07 mmol, 66% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.20 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.86-7.75 (m, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.26-7.10 (m, 3H), 6.84-6.70 (m, 1H), 3.93 (t, J = 3.0 Hz, 1H), 3.20 (t, J = 5.0 Hz, 1H), 2.80 (dd, J = 5.0, 3.0 Hz, 1H), 1.52 (s, 9H).

Step 3: (2-{4-[1-Hydroxy-2-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (**295**) and (2-{4-[2-Hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (**293**)

**[0352]** To a stirred solution of CoCl<sub>2</sub> (8 mg, 0.06 mmol) in dry acetonitrile (10 mL) was added **292** (1 g, 2.8 mmol) followed by 3,4,5-trimethoxyaniline (516 mg, 2.8 mmol) and the reaction mixture was allowed to react for 16 h at room temperature then it was heated at 60°C for 5 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/Hexane: 1/1) to afford compounds **293** and **295** (combined: 1.07 g, 1.99 mmol, 71% yield, ratio **292/295** = 5/1) which can be separated by flash chromatography on silica gel (AcOEt/Hexane: 1/1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): Compound **292**: 9.21 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.28-7.10 (m, 3H), 6.90 (s, 1H), 5.83 (s, 2H), 4.54-4.44 (m, 1H), 3.93 (dd,

J = 8.1, 3.9 Hz, 1H), 3.84-3.72 (m, 1H), 3.71 (s, 3H), 3.66 (s, 6H), 1.47 (s, 9H). Compound 295: 9.22 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.30-7.21 (m, 3H), 6.88 (s, 1H), 6.15 (s, 2H), 5.16-5.06 (m, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.50-3.25 (m, 2H), 1.51 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzamide (294)

**[0353]** Following a procedure analogous to that described in Example 42, step 3, but substituting **293** for **46**, the title compound **294** was obtained in 50% yield. <sup>1</sup>H NMR (DMSO) δ (ppm): 8.36 (s, 1H), 7.74 (d, J = 6.9 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.72 (m, 2H), 5.69 (s, 2H), 4.34 (m, 1H), 4.02-3.52 (m, 2H), 3.66 (s, 3H), 3.57 (s, 6H).

### Example 170

Step 1: N-(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-4-yl]-benzamide (296)

**[0354]** To a solution of **293** (200 mg, 0.372 mmol) in toluene (5 mL) and THF (1 mL) was added 1,1'-carbonyldiimidazole (72 mg, 0.45 mmol) followed by Et<sub>3</sub>N (156 μL, 1.12 mmol) and the mixture was stirred at room temperature for 5 h then at 90°C for 48 h. The reaction mixture was diluted with AcOEt, a solution of sat. NH<sub>4</sub>Cl was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (DCM/AcOEt: 80/20) to afford the desired compound (120 mg, 0.21 mmol, 57% yield). <sup>1</sup>H NMR (DMSO) δ (ppm): 9.37 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.25-15 (m, 3H), 6.88 (s, 1H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.79 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 6H), 1.47 (s, 9H).

**[0355]** Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **296** was obtained in 81% yield. <sup>1</sup>H NMR (DMSO) δ (ppm): 8.03 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.78 (t, J = 8.7 Hz, 1H), 4.18 (dd, J = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H).

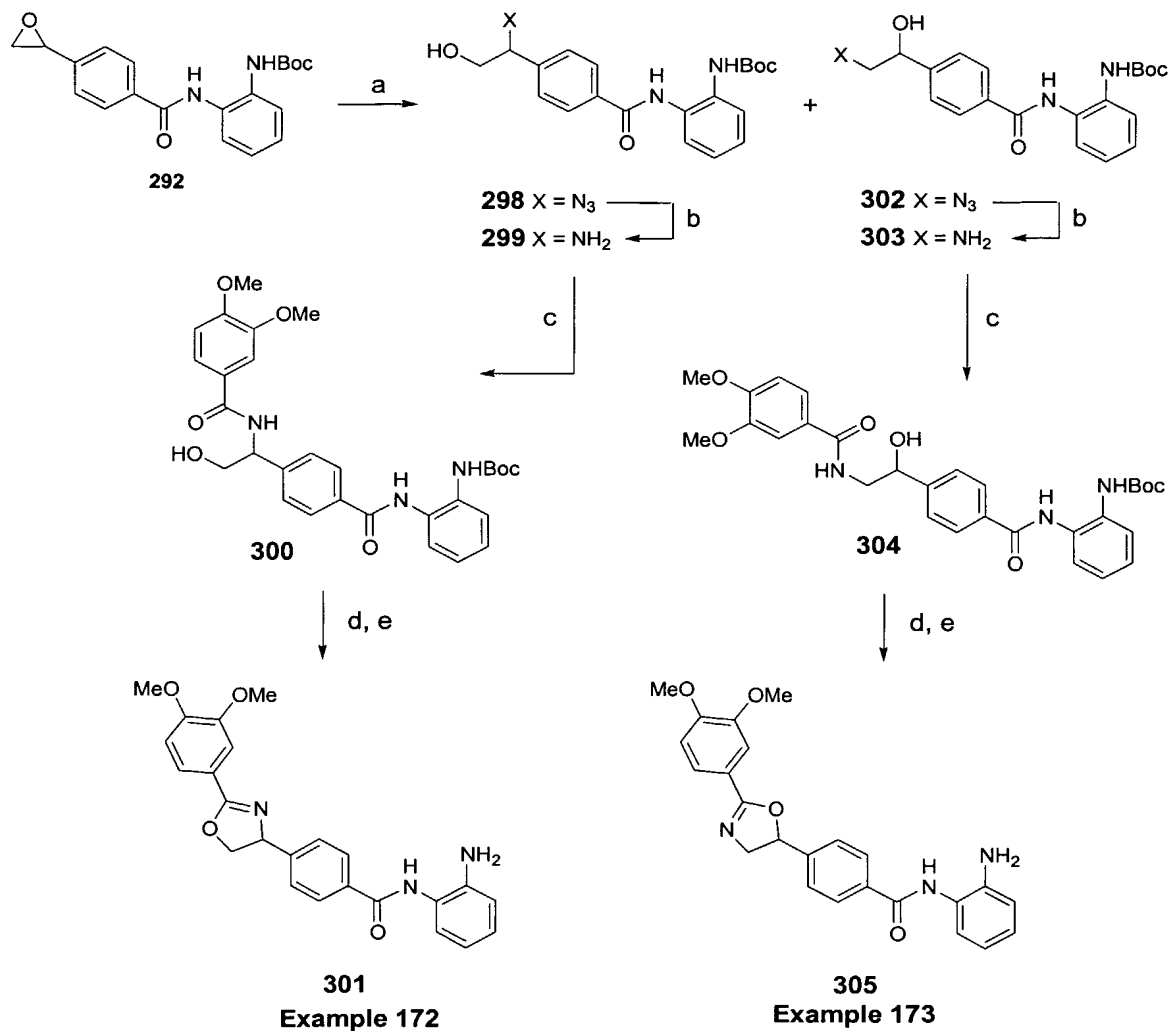
**Example 171**

Step 1: N(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-5-yl]-benzamide (297)

**[0356]** To a solution of **295** (130 mg, 0.242 mmol) in DCM (2 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol) and the mixture was stirred at room temperature for 16 h. DCM was removed under reduced pressure, AcOEt and a solution of sat. NH<sub>4</sub>Cl were added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (Hexane/AcOEt: 30/70) to afford the desired compound (80 mg, 0.14 mmol, 58% yield). <sup>1</sup>H NMR (DMSO) δ (ppm): 9.39 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.26-7.12 (m, 3H), 6.86-6.74 (m, 3H), 5.70 (t, J = 8.4 Hz, 1H), 4.24 (t, J = 8.7 Hz, 1H), 3.97-3.87 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 1.52 (s, 9H).

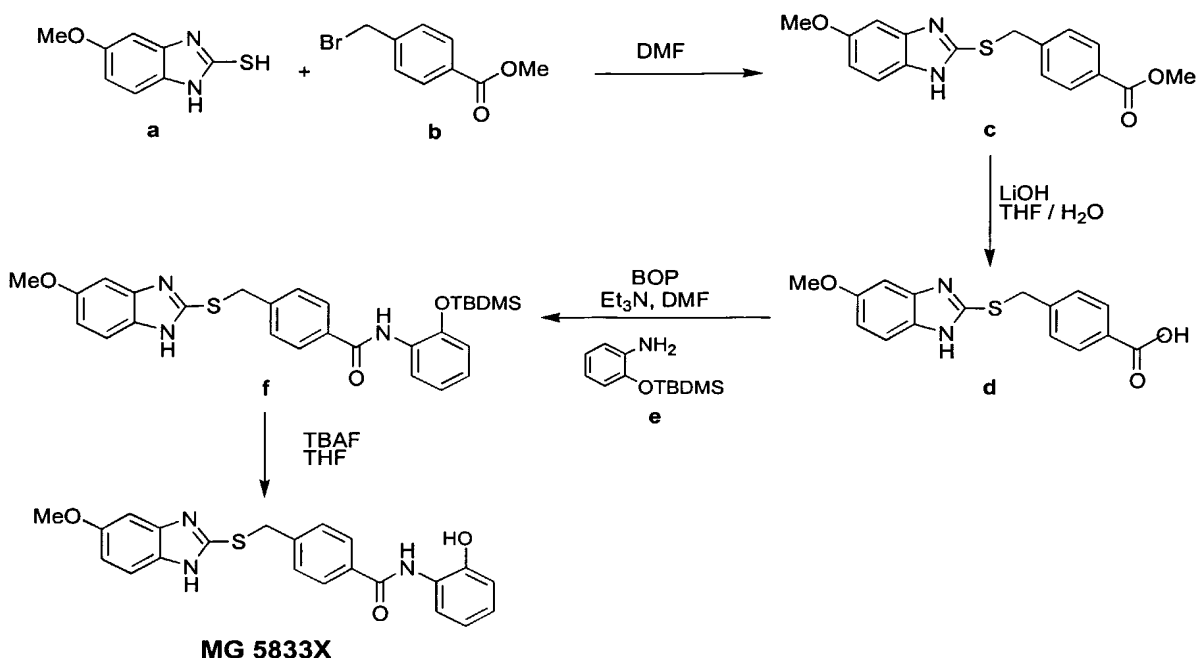
**[0357]** Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **297** was obtained in 94% yield. <sup>1</sup>H NMR (DMSO) δ (ppm): 8.38 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.97-6.87 (m, 2H), 6.79 (s, 2H), 5.66 (t, J = 8.1 Hz, 1H), 4.41 (t, J = 9.0 Hz, 1H), 3.91 (t, J = 7.8 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H).

## Scheme 54



- a. CeCl<sub>3</sub> heptahydrate / NaN<sub>3</sub> / CH<sub>3</sub>CN - H<sub>2</sub>O (9 : 1) / reflux  
 b. H<sub>2</sub> / Pd/C (10%) / MeOH  
 c. 3,4-dimethoxybenzoyl chloride / Et<sub>3</sub>N / DCM / -20°C to r.t.  
 d. Burgess reagent / THF / 70°C  
 e. TFA / DCM

Scheme 55



## Example 172

Step 1: {2-[4-(1-Azido-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**298**) and {2-[4-(2-Azido-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**302**)

**[0358]** To a solution of **292** (210 mg, 0.59 mmol) in acetonitrile (9 mL) and water (1 mL) was added  $\text{CeCl}_3$  heptahydrate (110 mg, 0.296 mmol) followed by  $\text{NaN}_3$  (42 mg, 0.65 mmol). The reaction mixture was refluxed for 3 h then acetonitrile was removed under reduced pressure. The residue was diluted with DCM, washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification by flash chromatography on silica gel (AcOEt/Hexane: 1/1) afforded a 1:1 mixture of title compounds **298** and **302** (combined: 187 mg, 0.47 mmol, 80% yield) which were separated by flash chromatography on silica gel (AcOEt/Hexane: 2/5). Compound **298**:  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.95 (d,  $J$  = 8.1 Hz, 2H), 7.70-7.63 (m, 1H), 7.43 (d,  $J$  = 8.1 Hz, 2H), 7.36-7.29 (m, 1H), 7.24-7.14 (m, 2H), 4.69 (dd,  $J$  = 7.5, 4.8 Hz, 1H), 3.80-3.65 (m, 2H), 1.49 (s, 9H). Compound **302**:  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 9.28 (s, 1H), 7.86 (d,  $J$  = 8.4 Hz, 2H), 7.71 (d,  $J$  = 7.5 Hz, 1H), 7.38 (d,  $J$  = 8.4 Hz, 2H), 7.25-7.08 (m, 3H), 7.01 (s, 1H), 4.87 (dd,  $J$  = 6.9, 5.1 Hz, 1H), 3.47-3.38 (m, 2H), 3.32-3.21 (bs, 1H), 1.50 (s, 9H).



Step 2: {2-[4-(1-Amino-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**299**)

**[0359]** To a solution of **298** (156 mg, 0.39 mmol) in MeOH (2 mL) was added Pd/C 10% (20 mg, 0.02 mmol). The reaction mixture was stirred under a 1 atm pressure of H<sub>2</sub> at room temperature for 16 h then it was purged with N<sub>2</sub>. The palladium was removed by filtration through celite and the MeOH was evaporated under reduced pressure to afford the title compound **299** (88 mg, 0.24 mmol, 60% yield), which was used without purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.24 (s, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.31-7.10 (m, 3H), 7.06-6.94 (m, 1H), 4.12 (dd, J = 7.5, 4.5 Hz, 1H), 3.74 (dd, J = 7.8, 5.4 Hz, 1H), 3.64-3.51 (m, 1H), 2.64 (s, 3H), 1.49 (s, 9H).

Step 3: (2-[4-[1-(3,4-Dimethoxy-benzoylamino)-2-hydroxy-ethyl]-benzoylamino]-phenyl)-carbamic acid tert-butyl ester (**300**)

**[0360]** To a stirred solution of **299** (88 mg, 0.24 mmol) in dry DCM (2 mL) at -20°C was added 3,4-dimethoxybenzoyl chloride (50 mg, 0.25 mmol) followed by Et<sub>3</sub>N (37 µL, 0.26 mmol). The reaction mixture was allowed to warm up to room temperature then was stirred for 48 h. A solution of sat. NH<sub>4</sub>Cl was added, followed by DCM and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 4/96) to afford title compound **300** (91 mg, 0.17 mmol, 71% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.29 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.46 (m, 7H), 6.80 (d, J = 8.1 Hz, 1H), 5.20-5.10 (m, 1H), 3.95-3.78 (m, 2H), 3.88 (s, 3H) 3.84 (s, 3H), 1.47 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-4-yl]-benzamide (**301**)

**[0361]** To a solution of **300** (91 mg, 0.17 mmol) in dry THF (2 mL) was added the Burgess reagent (44 mg, 0.19 mmol) and the mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 3/97) to afford the Boc-protected intermediate (75 mg, 0.14 mmol, 85% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 9.31 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.0 Hz, 1H), 7.23-7.08 (m, 3H), 6.93 (d, J = 8.7 Hz, 1H), 5.43 (t, J = 9.0 Hz, 1H), 4.84 (t, J = 9.3 Hz, 1H), 4.26 (t, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.50 (s, 9H).

**[0362]** Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **301** was obtained in 82%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.01 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.65 (dd, J = 8.4, 1.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 6.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 5.43 (dd, J = 9.7, 8.4 Hz, 1H), 4.83 (dd, J = 9.7, 8.4 Hz, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

### Example 173

Step 1: {2-[4-(2-Amino-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**303**)

**[0363]** The title compound **303** was obtained in 94% yield from **302** following the same procedure as in Example 172, step 2. The compound **303** was used directly for next step without purification.

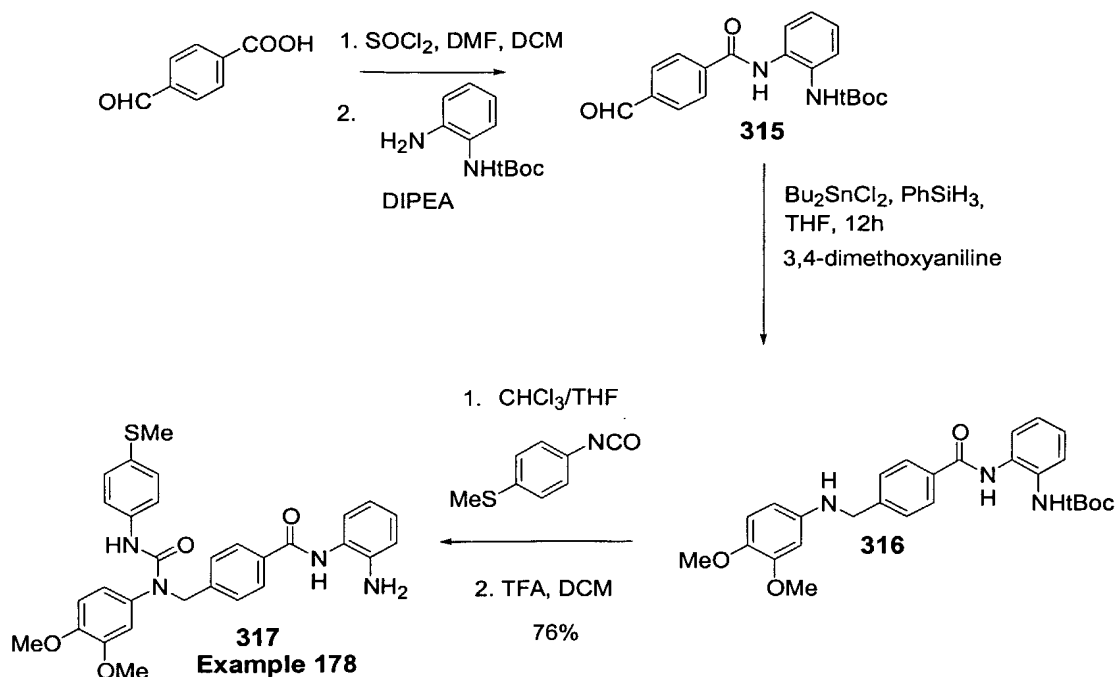
Step 2: 2-[4-[2-(3,4-Dimethoxy-benzoylamino)-1-hydroxy-ethyl]-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**304**)

**[0364]** The title compound **304** was obtained in 40% yield from **303** and 3,4-dimethoxybenzoyl chloride following the same procedure as in Example 172, step 3. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 9.31 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 8.1 Hz), 7.30-7.06 (m, 4H), 7.00-6.93 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.89-4.82 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85-3.73 (m, 1H), 3.44-3.32 (m, 1H), 1.46 (s, 9H).

Step 3: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-5-yl]-benzamide (**305**)

**[0365]** Following a procedure analogous to that described in Example 172, step 4, 5, but substituting **304** for **300**, the title compound **305** was obtained in 63%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.02 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 8.4, 1.8 Hz, 1H), 7.60 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 5.74 (dd, J = 10.0, 7.8 Hz, 1H), 4.51 (dd, J = 14.5, 10.0 Hz, 1H), 4.00-3.90 (m, 7H).

**Scheme 57**



**Example 178**

**STEP 1: [2-(4-FORMYL-BENZOYLAMINO)-PHENYL]-CARBAMIC ACID *tert*-BUTYL ESTER (**315**)**

**[0366]** To a suspension of 4-carboxybenzaldehyde (6 g, 40 mmol) in dichloromethane (10 mL) was added thionyl chloride (4.1 mL, 56 mmol, 1.4 eq), followed by DMF (1 mL) dropwise. The mixture was refluxed for 4 hours and excess of thionyl chloride and DMF were removed under reduced pressure. To a solution of (2-aminophenyl)-carbamic acid *tert*-butyl ester (8.32 g, 40 mmol, 1 eq) in dichloromethane (80 mL), stirred at 0°C, was added a suspension of 4-formyl benzoyl chloride in dichloromethane (20 mL), followed by diisopropyl ethylamine (3.61 mL, 20 mmol, 1 eq). The mixture was stirred for 30 minutes at 0°C then at room temperature for 30 minutes. The crude residue was diluted with dichloromethane (300 mL) and washed with water. The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated under vacuo. The crude residue was purified by column chromatography on silica gel (elution 20% ethyl acetate in hexane) to give 6.1 g (45% yield) of anilide **315**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.18 (s, 1H), 9.64 (brs, 1H), 8.20 (d,  $J = 7.9$  Hz, 2H), 8.06 (d,  $J = 7.9$  Hz, 2H), 7.96 (d,  $J = 7.9$  Hz, 1H), 7.28-7.38 (m, 1H), 7.24 (d,  $J = 4.4$  Hz, 1H), 6.84 (s, 1H), 6.81 (d,  $J = 8.8$  Hz, 1H), 1.58 (s, 9H).

Step 2: (2-{4-[(3,4-Dimethoxyphenylamino)-Methyl]-Benzoylamino}-Phenyl)-Carbamic Acid Tert-Butyl Ester (**316**)

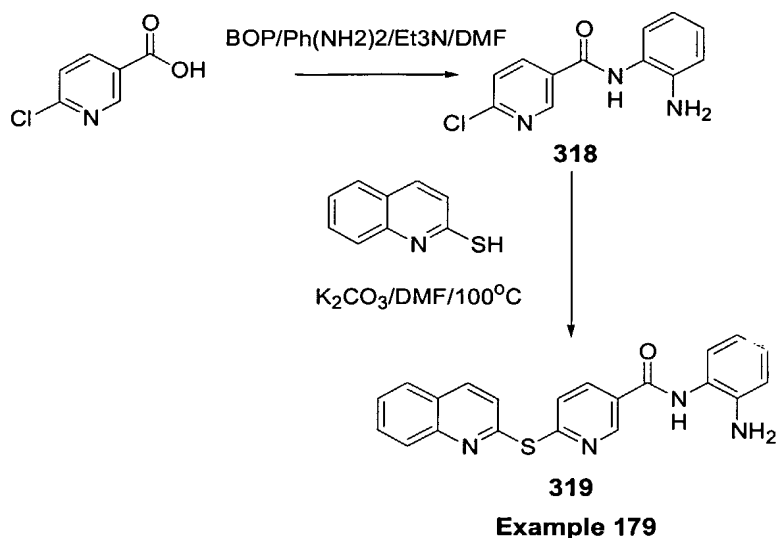
**[0367]** Following a procedure analogous to that described in Example 144, step 3, but substituting the previous compound for 226, the title compound **316** was obtained in quantitative yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.21 (brs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.20-7.34 (m, 3H), 6.89 (brs, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.23 (dd, J = 2.6, 8.3 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H).

Step 3: N-(2-Aminophenyl)-4-[1-(3,4-dimethoxyphenyl)-3-(4-methylsulfanylphenyl)-ureidomethyl]-benzamide **317**

**[0368]** To a solution of anilide **316** (500 mg, 1.047 mmol) in chloroform/THF<sup>-</sup> (1:1, 10 mL) was added isocyanate (169 μL, 1.205 mmol, 1.15 eq). The mixture was stirred overnight at room temperature under nitrogen and the crude residue was concentrated and purified by column chromatography on silica gel (elution 40% ethyl acetate in hexane) to give 606 mg (90% yield) of the desired compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.25 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.20-7.36 (m, 6H), 6.93 (d, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 2.2, 8.3 Hz, 1H), 6.68 (dd, J = 2.6 Hz, 1H), 6.33 (s, 1H), 5.0 (s, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.51 (s, 3H), 1.57 (s, 9H).

**[0369]** Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **317** was obtained in 85% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.14 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.93 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39 (d, J = 7.5 Hz, 1H), 7.10-7.30 (2m, 5H), 6.97 (dd, J = 2.2, 8.35 Hz, 1H), 6.77 (dd, J = 2.2, 8.35 Hz, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.48 (s, 3H).

## Scheme 58



## Example 179

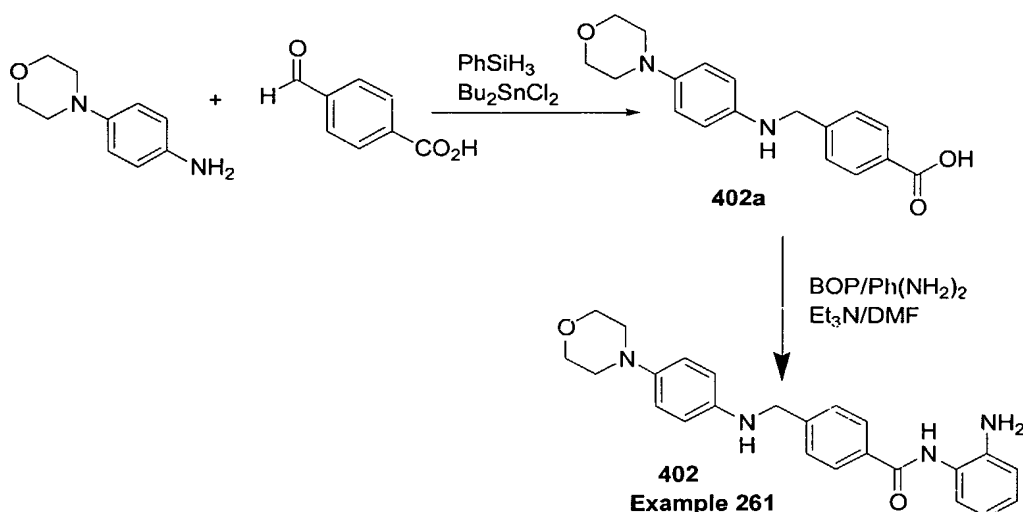
Step 1: N-(2-Amino-phenyl)-6-chloro-nicotinamide (**318**)

**[0370]** Following the procedure described in Example 42, step 2, the title compound **318** was obtained in 80% yield. LRMS = calc:246.69, found:247.7.

Step 2: N-(2-Amino-phenyl)-6-(quinolin-2-ylsulfanyl)-nicotinamide (**319**)

**[0371]** Following the procedure described in Example 45, step 1 but substituting **318** for 3,4,5-trimethoxybenzylamine, the title compound **319** was obtained in 20% yield. <sup>1</sup>H NMR: (CD<sub>3</sub>OD-d<sub>6</sub>) δ (ppm): 9.08 (d, J = 1.9 Hz, 1H), 8.35-8.25 (m, 2H), 7.99-7.56 (m, 7H), 7.23 (dd, J = 1.2, 7.9 Hz, 1H), 7.12 (dd, J = 1.4, 7.9, 14.0 Hz, 1H), 6.93 (dd, J = 1.2, 8.0 Hz, 1H), 6.79 (ddd, J = 1.4, 7.7, 13.7 Hz, 1H).

## Scheme 59

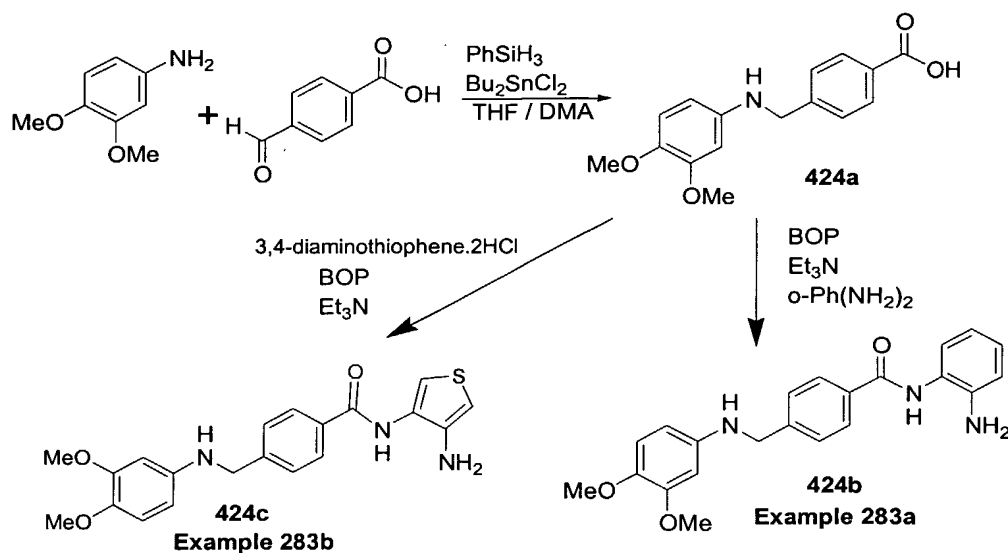
Step 1: 4-[(4-Morpholin-4-yl-phenylamino)-methyl]-benzoic acid (**402a**).

**[0372]** A suspension of 4-formylbenzoic acid (2.53g; 16.8 mmol; 1 eq), 4-morpholinoaniline (3g; 16.8 mmol; 1 eq) and  $\text{Bu}_2\text{SnCl}_2$  (510 mg; 1.68 mmol; 0.1 eq) in dry THF (20 ml) was treated with  $\text{PhSiH}_3$  (3.31ml; 16.8 mmol; 1 eq) at room temperature for 12 h. The reaction was filtered and the solid product was washed with MeOH. The yield of the reaction was 5.25g (99%). LRMS: calc 312.37; found: 313.2.

Step 2: N-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide (**402**)

**[0373]** To a solution of acid **402a** (2.61g; 8.36 mmol; 1 eq), 1,2-phenylenediamine (903 mg; 8.36 mmol; 1 eq) and BOP (3.70g; 8.36 mmol; 1 eq) in dry DMF (20 ml) was added  $\text{Et}_3\text{N}$  (4.64ml; 33.4 mmol; 4 eq). After stirring overnight most of the DMF was removed under reduced pressure and chromatographed (Hex:EtAcO: 1:2/ EtAcO). The crystal **402** was obtained in 70% (2.35g).  $^1\text{H}$ -NMR (300.07 MHz;  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.65 (s, 1H), 7.97 (d,  $J=7.9$ , 2H), 7.53 (d,  $J=7.9$ , 2H), 7.22 (d,  $J=7.5$ , 1H), 7.03 (dd,  $J=7.0$ , 7.5, 1H), 6.83 (d,  $J=7.9$ , 1H), 6.77 (d,  $J=8.8$ , 2H), 6.65 (dd,  $J=7.5$ , 7.0, 1H), 6.57 (d,  $J=8.8$ , 2H), 4.93 (bs, 2H), 4.36 (d,  $J=5.7$ , 2H), 3.75 (m, 4H), 2.93 (m, 4H). LRMS: calc 402.49; found: 403.4.

## Scheme 60



## Example 283a

Step 1. 4-[(3,4-Dimethoxyphenylamino)-methyl]-benzoic acid (424a)

**[0374]** In a 50 ml flask, a mixture of 4-aminoveratrole (1.53 g, 10 mmol), 4-formyl-benzoic acid (1.50 g, 10 mmol), dibutyltin dichloride (304 mg, 1 mmol), phenylsilane (2.47 ml, 20 mmol) in anhydrous THF (10 mL) and DMA (10 ml) was stirred overnight. at room temperature. After solvents removal, the crude residue was dissolved in ethyl acetate (100 ml) and then washed with saturated aqueous solution of NaHCO<sub>3</sub> (50 ml x 3) . The combined aqueous layers were acidified with 6% of NaHSO<sub>4</sub> to pH = 4. The resulting white suspension was filtrated and then the filter cake was washed with water (5 ml x 3). The cake was dried over freeze dryer to afford acid (1.92 g, 67 %) white solid product. LRMS = 288 (MH)<sup>+</sup>.

Step 2. N-(2-Aminophenyl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide (424b)

**[0375]** In a 150 ml flask, a mixture of acid (1.92 g, 6.69 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 3.26 g, 7.37 mmol), triethylamine ( 1.87 ml, 13.4 mmol), o-phenylenediamine (1.30g, 12.02 mmol) in methylenechloride ( 67 ml) was stirred at rt for 2 h. After solvents removal, the crude residue was dissolved in EtOAc (100 ml) and then washed with NaHCO<sub>3</sub> saturated solution and brine 50 ml. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the filtrate was concentrated to dryness. The crude material was submitted to a chromatographic purification (column silica, 55%-70 % EtOAc in 1% Et<sub>3</sub>N of hexanes) and then the all interested fractions were concentrated to dryness. The residue was suspended in minimum

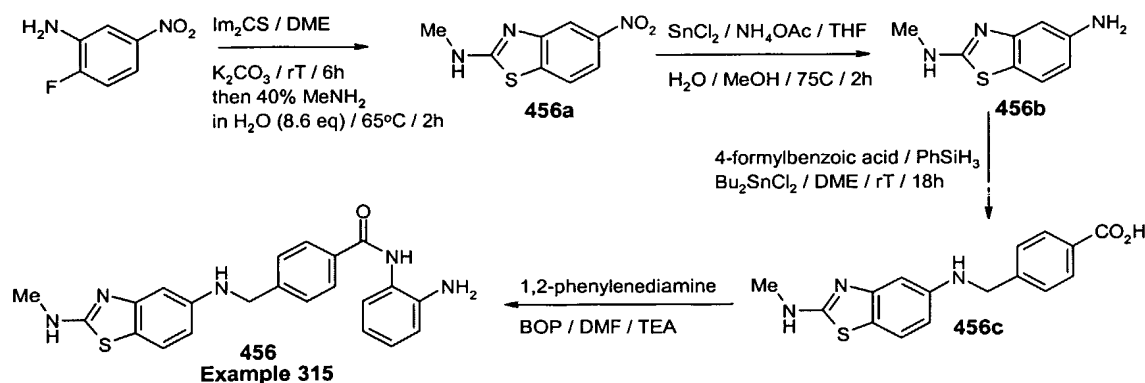
quantities of ethyl acetate and then filtered to afford final product (1.49 g, 59 %).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm): 9.65 (s, 1H), 7.98 (d,  $J$  = 7.9 Hz, 2H), 7.54 (d,  $J$  = 7.9 Hz, 2H), 7.22 (d,  $J$  = 7.9 Hz, 1H), 7.02 (dd,  $J$  = 7.9, 7.9 Hz, 1H), 6.83 (d,  $J$  = 7.9 Hz, 1H), 6.72 (d,  $J$  = 8.79 Hz, 1H), 6.45 (dd,  $J$  = 7.5, 7.5 Hz, 1H), 6.39 (d,  $J$  = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H,  $\text{NH}_2$ ), 4.36 (d,  $J$  = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).

### Example 283b

Step 1: N-(4-Aminothiophen-3-yl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide:

**[0376]** Acid **424a** (1040 mg; 3.62 mmol); 3,4-diaminothiophene dihydrochloride (1017 mg; 5.44 mmol; 1.50 eq.) and BOP (1770 mg; 4.0 mmol; 1.1 eq.) were suspended in MeCN, treated with triethylamine (4 mL; 29 mmol) and stirred for 18h at room temperature; concentrated and purified by chromatographic column on silica gel (elution 50% EtOAc in DCM) to render 527 mg (1.37 mmol; 38 % yield) of compound **424c** which was 90% pure.  $^1\text{H}$ -NMR (300.07 MHz; DMSO- $d_6$ )  $\delta$  (ppm): 8.56 (s, 1H), 7.78 (d,  $J$ =7.9 Hz, 2H), 7.43 (d,  $J$  = 3.5 Hz, 1H), 7.38 (d,  $J$  = 7.9 Hz, 2H), 6.73 (d,  $J$  = 8.8 Hz, 1H), 6.33 (d,  $J$  = 3.5 Hz, 1H), 6.58 (d,  $J$  = 2.6 Hz, 1H), 6.13 (dd,  $J$  = 2.6, 8.3 Hz, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). LRMS: calc: 383.4642; found: 384.2 (M+H); 406.2 (M+Na) and 192.6 (M+2H)/2.

### Scheme 61



Step 1: Methyl-(5-nitrobenzothiazol-2-yl)-amine (**456a**)

**[0377]** A mixture of 2-fluoro-5-nitroaniline (861 mg; 5.52 mmol; 1.02 eq);  $\text{Im}_2\text{CS}$  (960.3 mg; 5.39 mmol) and dry  $\text{K}_2\text{CO}_3$  (1.45g) was suspended in dry DME (10 mL) and stirred under nitrogen for 90 min at room temperature. The yellow suspension was made fluid by diluting with DME (10 mL) followed by addition of 40% MeNH $_2$  in water (4.0 mL; 46.5 mmol; 8.6 eq). The system was heated up



to 65°C and stirred at this temperature for 3.5 h, cooled down, diluted with ethyl acetate and washed with saturated NaCl (X2). After conventional work-up procedures, the dark crude mixture was purified through chromatographic column on silica gel (elution 50% EtOAc in hexane, then 5% MeOH in DCM), to afford 836.8 mg (4.0 mmol; 72% yield) of compound **456a**.

Step 2: N-Methyl-benzothiazole-2,5-diamine (**456b**)

**[0378]** A mixture of nitro compound **456a** (593 mg; 2.83 mmol); SnCl<sub>2</sub> (4.02 g; 20.8 mmol; 7.35 eq) and NH<sub>4</sub>OAc (4.5g) was suspended in THF:MeOH:H<sub>2</sub>O = 1:1:1 (60 mL) and stirred at 70°C for 2 h, cooled down, diluted with ethyl acetate and successively washed with saturated NaHCO<sub>3</sub> and brine; dried (MgSO<sub>4</sub>) filtered and concentrated. The residue (443 mg; 2.43 mmol; 87%) showed consistent spectrum and suitable purity degree for synthetic purposes, therefore was submitted to the next step without further purification.

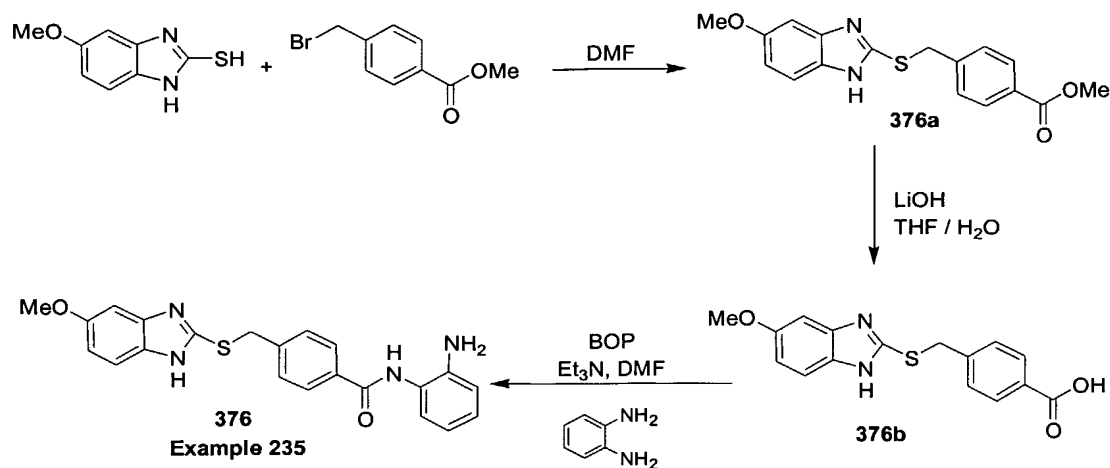
Step 3: 4-[(2-Methylaminobenzothiazol-5-Ylamino)-Methyl]-Benzoic Acid (**456c**)

**[0379]** A solution of aniline **456b** (509 mg; 2.8 mmol); 4-formylbenzoic acid (426 mg; 2.8 mmol) and Bu<sub>2</sub>SnCl<sub>2</sub> (198 mg; 0.65 mmol; 23% mol) in DME (14 mL) was stirred at room temperature for 3 min and treated with neat PhSiH<sub>3</sub> (0.6 mL; 4.7 mmol; 1.7 mmol) and allowed to react for 18h. After quenching the excess of silane with MeOH, the mixture was concentrated and purified by chromatographic column on silica gel (elution 5% MeOH in DCM) to give 729 mg (2.54 mmol; 91% yield) of acid **456c**.

Step 4: N-(2-Aminophenyl)-4-[(2-methylaminobenzothiazol-5-ylamino)-methyl]-benzamide (**456**)

**[0380]** A mixture of acid **456c** (729 mg; 2.54 mmol), 1,2-phenylenediamine (376 mg; 3.47 mmol; 1.36 eq) and BOP (1.43 g; 3.23 mmol; 1.27 eq) was dissolved in acetonitrile (15 mL), treated with triethylamine (3mL) and stirred overnight. The reaction mixture was quenched with methanol, concentrated and purified by chromatographic column on silica gel (40% EtOAc in DCM) and the obtained material crystallized from DCM to give 358 mg (0.88 mmol; 35 % yield) of pure compound **456**. <sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>) δ (ppm): 9.57 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.76 4.87 (bs, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.13 (dd, J = 1.8, 8.3 Hz, 1H), 6.27 (t, J = 5.7 Hz, 1H), 4.87 (bs, 2H), 4.36 (d, J = 5.7 Hz, 2H), 2.85 (d, J = 4.8 Hz, 3H). LRMS: calc: 403.5008, found: 404.2 (M+NH) and 202.6 (M+2H)/2.

## Scheme 62



## Example 235

Step 1: Methyl-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoate (**376a**)

**[0381]** To a solution 5-methoxy-2-thiobenzimidazole (2.00 g, 11.1 mmol) in anhydrous DMF (40 ml) was added methyl-4-(bromomethyl)-benzoate (2.54 g, 11.1 mmol). The reaction mixture was stirred 16 h at room temperature. The DMF was evaporated and the residue was triturated in ethyl acetate during 30 min and then filtered and dried. The desired compound was isolated as the HBr salt: 98% yield, (4.44 g). <sup>1</sup>H NMR: (DMSO) δ (ppm): 7.90 (d, J = 8.8 Hz, 2H), 7.56-7.52 (m, 3H), 7.09 (d, J = 2.2 Hz, 1H), 7.01 (dd, J = 8.8, 2.2 Hz, 1H), 4.73 (s, 2H), 3.82 (s, 6H). MS: (calc.) 328.1, (obt.), 329.2 (MH)<sup>+</sup>.

Step 2: 4-(5-Methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid (**376b**)

**[0382]** A solution of LiOH.H<sub>2</sub>O (1.02 g, 24.4 mmol) in water (15 ml) was added to a suspension of **376a** (3.99 g, 9.75 mmol) in THF (10 ml). The reaction mixture was stirred 16 h at room temperature. The reaction mixture was acidified with a solution of HCl 1 M to pH 4. The desired product was triturated 20 min. at 0°C and then filtered and dried. Compound **376b** was obtained as a white powder (100% yield, 3.05 g). <sup>1</sup>H NMR: (DMSO) δ (ppm): 12.85 (bs, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.8, 2.2 Hz, 1H), 4.60 (s, 2H), 3.82 (s, 3 H). MS: (calc.) 314.1, (obt.), 315.1 (MH)<sup>+</sup>.

Step 3: *N*-(2-Amino-phenyl)-4-(5-methoxy-1*H*-benzimidazol-2-yl-sulfanylmethyl)-benzamide (**376**)

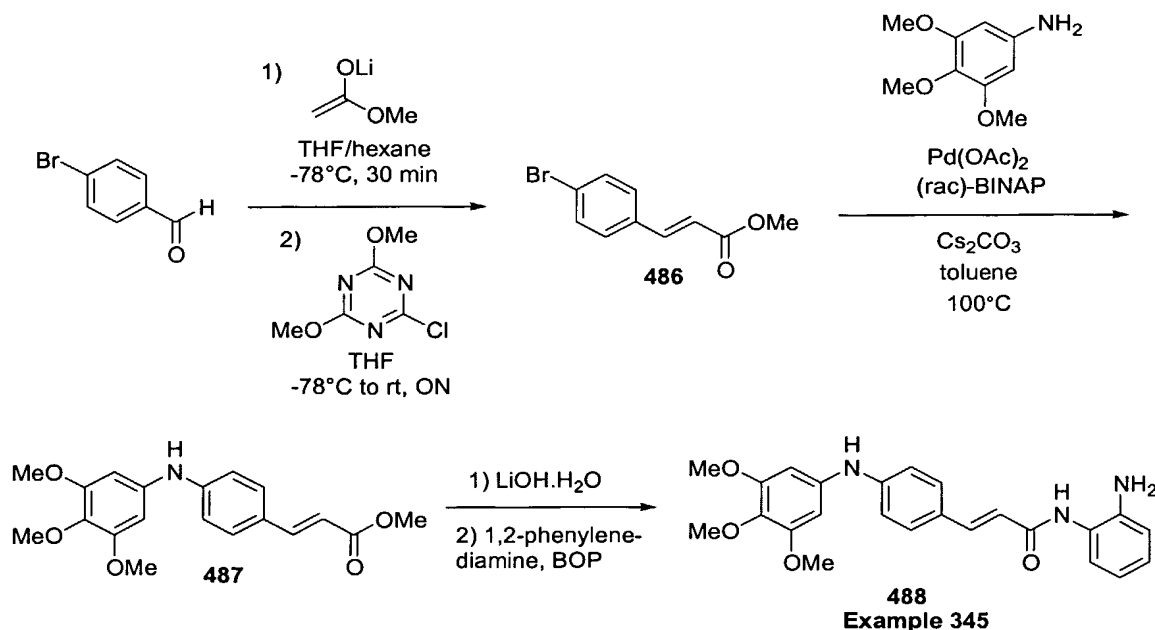
[0383] Following the procedure described in Example 1 step 5 but substituting 4-(5-methoxy-1*H*-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid **2** for **7** the title compound **376** was obtained as a white powder.: 36% yield (933 mg). <sup>1</sup>H NMR: (DMSO)  $\delta$  (ppm): 12.42 (bs, 1H), 9.57 (bs, 1H), 7.89 (d,  $J$  = 8.1 Hz, 2H), 7.55 (d,  $J$  = 8.1 Hz, 2H), 7.34 (d,  $J$  = 8.8 Hz, 1H), 7.14 (d,  $J$  = 7.3 Hz, 1H), 6.98-6.93 (m, 2H), 6.77-6.55 (m, 2H), 6.58 (dd,  $J$  = 7.3, 7.3 Hz, 1H), 4.87 (s, 2H), 4.59 (s, 2H), 3.77 (s, 3 H). MS: (calc.) 404.1, (obt.), 405.4 (MH)<sup>+</sup>.

**Examples 180-328**

[0384] Examples **180** to **327** (compounds **320** - **468**) were prepared using the same procedure as described for compound **126** to **319** in Example **85** to **179** (scheme **11** to **58**).

**Examples 329-344**

[0385] Examples **329** to **344** (compounds **470** - **485**) were prepared using the same procedure as described for compound **8** to **224** in Example **1** to **143** (scheme **1** to **32**).

**Scheme 63**

**Example 345****Step 1: Methyl 3-(4-bromo-phenyl)-acrylic ester (486)**

**[0386]** To a solution of anhydrous  $i\text{Pr}_2\text{NH}$  (758  $\mu\text{l}$ , 5.40 mmol) in anhydrous THF (25 ml) stirred at 0°C under nitrogen, was slowly added a solution of  $n\text{BuLi}$  (2.22 ml, 5.54 mmol, 2.5 M in hexane). After 30 min, LDA was cooled to -78°C and anhydrous methyl acetate (430  $\mu\text{l}$ , 5.40 mmol) was added dropwise. After 30 min, a solution of 4-bromobenzaldehyde (500 mg, 2.70 mmol) in anhydrous THF (10 ml) was slowly added. After 30 min, a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (569 mg, 3.24 mmol) in anhydrous THF (15 ml) was added. Then, the temperature was allowed to warm up to room temperature overnight. A suspension appeared. The reaction mixture was poured into a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ , and diluted with AcOEt. After separation, the organic layer was successively washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/hexane: 10/90) to give the title product **486** (394 mg, 1.9 mmol, 61% yield) as a colorless crystalline solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.63 (d,  $J$  = 16.2 Hz, 1H), AB system ( $\delta_{\text{A}}$  = 7.53,  $\delta_{\text{B}}$  = 7.39,  $J$  = 8.4 Hz, 4H), 6.43 (d,  $J$  = 15.8 Hz, 1H), 3.82 (s, 3H).

**Step 2: Methyl 3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylic ester (487)**

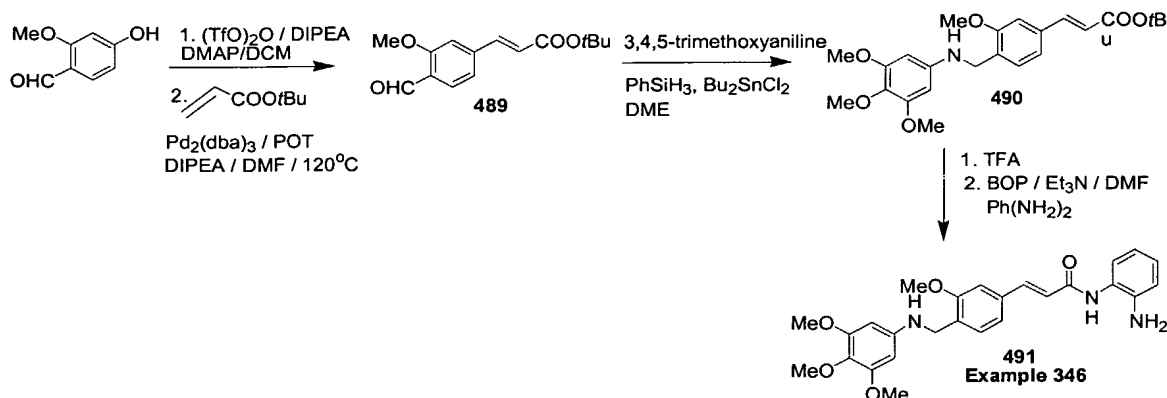
**[0387]** A mixture of  $\text{Cs}_2\text{CO}_3$  (378 mg, 1.16 mmol),  $\text{Pd}(\text{OAc})_2$  (6 mg, 0.025 mmol), (rac)-BINAP (23 mg, 0.037 mmol), was purged with nitrogen for 10 min. **486** (200 mg, 0.83 mmol), 3,4,5-trimethoxyaniline (182 mg, 0.99 mmol), and anhydrous toluene (5 ml) were added, respectively. The reaction mixture was heated to 100°C under nitrogen for 24 h. Then, it was allowed to cool to room temperature, diluted with AcOEt, and successively washed with a saturated aqueous solution  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$  and brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the title compound **487** (280 mg, 0.82 mmol, 98% yield) as a yellow oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.64 (d,  $J$  = 16.2 Hz, 1H), 7.43 (bd,  $J$  = 7.9 Hz, 2H), 7.12-6.86 (m, 2H), 6.60-6.20 (m, 3H, included at 6.29, d,  $J$  = 15.8 Hz), 3.84 (s, 9H), 3.80 (s, 3H).

**Step 3: N-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylamide (488)**

**[0388]** The title compound **488** was obtained from **487** in 2 steps following the same procedure as Example 1, steps 4 and 5.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm): 9.29 (s, 1H), 8.48 (s, 1H), 7.60-7.42 (m, 3H), 7.38 (d,  $J$  = 7.5 Hz, 1H), 7.12 (d,  $J$  = 8.4 Hz, 2H), 6.94 (t,  $J$  = 7.5 Hz, 1H), 6.78

(d, J = 7.9 Hz, 1H), 6.71 (d, J = 15.8 Hz, 1H), 6.61 (t, J = 7.1 Hz, 1H), 6.47 (s, 2H), 4.97 (s, 2H), 3.79 (s, 6H), 3.66 (s, 3H).

### Scheme 64



### Example 346

#### Step 1: 3-(4-Formyl-3-methoxy-phenyl)-acrylic acid tert-butyl ester **489**

**[0389]** Following the procedure described in Example 53, step 1, but substituting 4-hydroxy-2-methoxy-benzaldehyde for **84**, followed by Example 42, step 2, but substituting the previous compound for **42**, the title compound **489** was obtained in 29% yield. LRMS = calc: 262, found: 263.2 (M+H<sup>+</sup>).

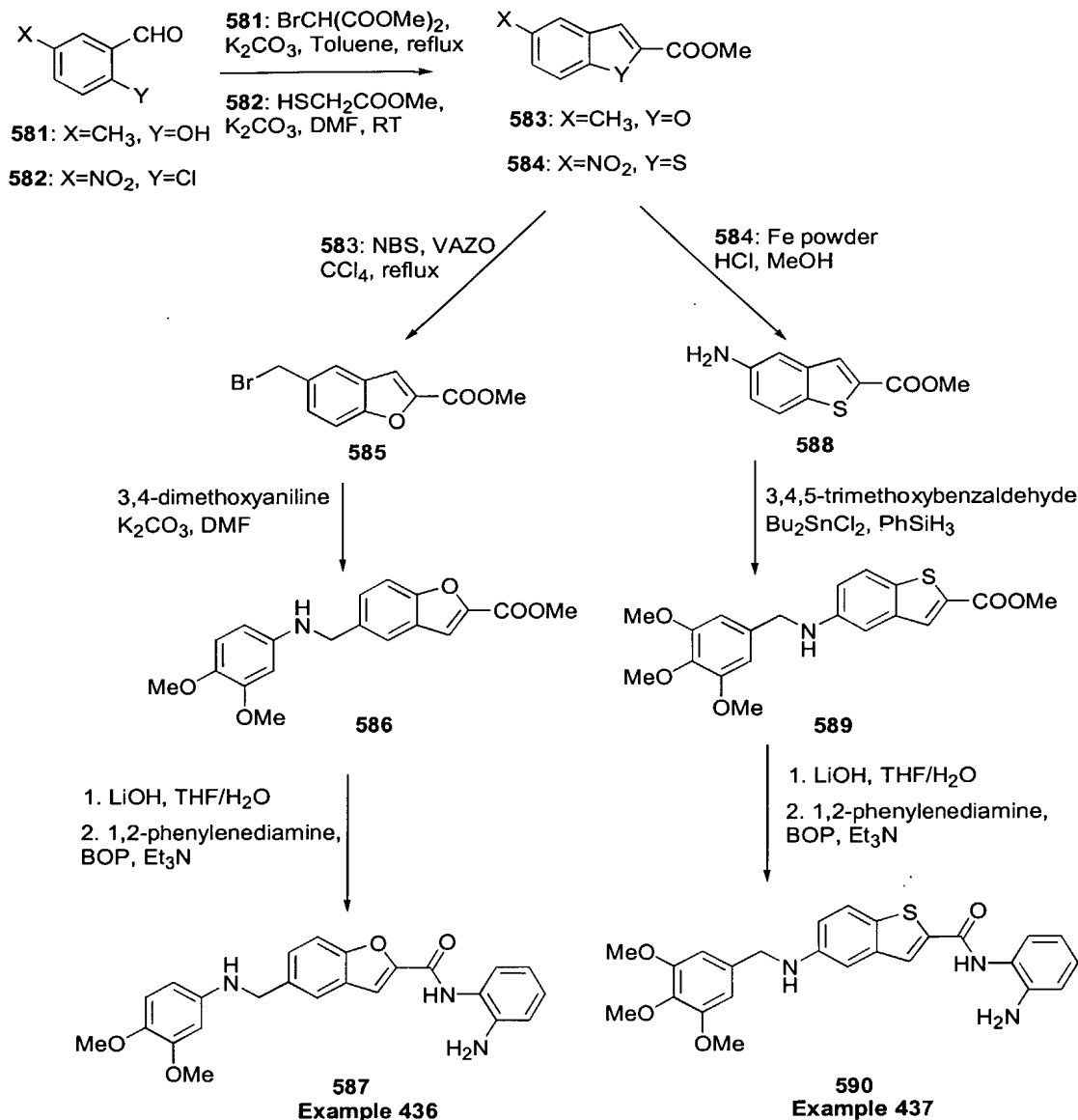
#### Step 2: 3-[3-Methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl]-acrylic acid tert-butyl ester **490**

**[0390]** Following the procedure described in Example 144, step 3, but substituting **489** for 4-formylbenzaldehyde, the title compound **490** was obtained in 69% yield. LRMS = calc: 429, found: 430.5 (M+H<sup>+</sup>).

#### Step 3: N-(2-Amino-phenyl)-3-[3-methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl]-acrylamide **491**

**[0391]** Following the procedure described in Example 42, step 3, 4, but substituting **490** for **46**, the title compound **491** was obtained in 67% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ (ppm): 8.08 (s, 1H), 7.74 (d, J = 15.4 Hz, 1H), 7.30 (m, 1H), 7.06 (m, 3H); 6.80 (m, 3H), 6.70 (d, J = 15.4 Hz, 1H), 5.98 (s, 2H), 4.40 (s, 2H); 4.12 (bs, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.77 (s, 6H).

## Scheme 65



## Example 436

Step 1: Methyl-5-methyl-benzofuran-2-carboxylate (**583**)

**[0392]** A stirring suspension of 5-methylsalicylaldehyde (1.0 mg, 7.5 mmol),  $\text{K}_2\text{CO}_3$  (1.55 g, 11.0 mmol), and  $\text{Bu}_4\text{NBr}$  (322 mg, 1 mmol) in toluene (30ml) was treated with dimethylbromomalonate (1.06 ml, 8.0 mmol). The suspension was heated to reflux with a Dean-Stark trap for 20 h. The brown

suspension was cooled to 25°C and concentrated in vacuo. The residue was taken in DCM and filtered. The filtrate was washed with H<sub>2</sub>O, 1N NaOH and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by column chromatography (10% ethyl acetate/hexane) to afford the title compound **583** (600mg, 42% yield). LRMS : 190.2 (Calc.); 191.1 (found).

Step 2: Methyl-5-bromomethyl-benzofuran-2-carboxylate (**585**)

**[0393]** A mixture of **583** (500 mg, 2.63 mmol), *N*-bromosuccinimide (561 mg, 3.15 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (Vazo) (63 mg, 0.26 mmol) in 15 ml of CCl<sub>4</sub> was heated overnight under reflux. The mixture was cooled to room temperature, quenched by adding water and extracted with DCM. The organic layer was washed with brine and dried over MgSO<sub>4</sub>, filtered and concentrated. The crude residue was purified by column chromatography (30% ethyl acetate/hexane) to afford the title compound **585** (680mg, 96% yield). <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ (ppm): 7.79 (s, 1H), 7.70-7.52 (m, 3H), 4.69 (s, 2H), 4.06 (s, 3H), 3.72 (s, 2H). LRMS : 268.2 (Calc.); 269.1 (found).

Step 3: Methyl-5-[(3,4-dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylate (**586**)

**[0394]** Following the procedure described in Example 47, step 2, but substituting **585** for **63**, the title compound **586** was obtained in 40% yield. LRMS : 341 (Calc.); 342.3 (found).

Step 4: 5-[(3,4-Dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (**587**)

**[0395]** Following the procedure described in Example 1, steps 4,5, but substituting **585** for **6**, the title compound **587** was obtained in 29% yield. <sup>1</sup>H NMR: (DMSO) δ (ppm): 9.83 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 5.5 Hz, 1H), 4.93 (s, 2H), 4.31 (d, J = 5.5 Hz, 1H), 2.82 (s, 3H), 2.76 (s, 3H). LRMS : 417.46 (Calc.); 418.4 (found).

### Example 437

Step 1: Methyl-5-nitro-benzo[b]thiophene-2-carboxylate (**584**)

**[0396]** A stirring suspension of 5-nitro-2-chloro-benzaldehyde (4.0 g, 21.6 mmol) in DMF (40 ml) at 5°C was treated with K<sub>2</sub>CO<sub>3</sub> (3.52 g, 25.5 mmol) followed by methylglycolate (1.93 ml, 21.6 mmol). The resulting solution was warmed to 25°C and stirred for 20h. The solution was then poured into 250ml of ice H<sub>2</sub>O and the white precipitate that formed was collected by filtration. Crystallization

from EtOAc afforded fine pale orange needles of **584** (3.54 g, 69%). LRMS : 237.0 (Calc.); 238.1 (found). <sup>1</sup>H NMR: (DMSO) δ (ppm): 9.00 (d, J = 2.2 Hz, 1H), 8.45 (s, 1H), 8.39-8.30 (m, 2H), 3.93 (s, 3H).

Step 2: Methyl-5-amino-benzo[b]thiophene-2-carboxylate (**588**)

[0397] A suspension of **584** (3.52 g, 14.8 mmol) in methanol (100 ml) was treated with Fe powder (6.63 g, 118.7 mmol). The resulting suspension was heated to reflux, and 12M HCl (8.5 ml) was slowly added over 15 min. The resulting green dark suspension was refluxed for an additional 3 h, then cooled and concentrated. The residue was taken up in EtOAc and washed with saturated aqueous NaHCO<sub>3</sub>, then brine, dried over MgSO<sub>4</sub>, filtered and concentrated to afford (2.57 g, 84%). <sup>1</sup>H NMR: (DMSO) δ (ppm): 7.92 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 1.8, 8.4 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H). LRMS : 207.0 (Calc.); 208.1 (found).

Step 3: Methyl-5-(3,4,5-trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylate (**589**)

[0398] Following the procedure described in Example 144, step 3, but substituting **588** for **226**, the title compound **589** was obtained in 68% yield. (DMSO) δ (ppm): 7.94 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.73 (s, 2H), 6.41 (t, J = 5.7 Hz, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 6H), 3.62 (s, 3H). LRMS : 387.1 (Calc.); 388.3 (found).

Step 4: 5-(3,4,5-Trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (**590**)

[0399] Following the procedure described in Example 1, steps 4,5, but substituting **589** for **6**, the title compound **590** was obtained in % yield<sup>1</sup>H NMR: (DMSO) δ (ppm): 7.79 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.00-6.95 (m, 2H), 6.74 (s, 2H), 4.32 (s, 2H), 3.80 (s, 6H), 3.73 (s, 3H).



### Examples 347-425

**[0393]** Examples **347** to **425** (compounds **492-570**) were prepared using the same procedure as described for compound **44** to **491** in Example **40** to **346** (scheme **3** to **64**).

### Assay Example 1

#### Inhibition of Histone Deacetylase Enzymatic Activity

##### 1. Human HDAC-1

**[0394]** HDAC inhibitors were screened against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system. For deacetylase assays, 20,000 cpm of the [<sup>3</sup>H]-metabolically labeled acetylated histone substrate (M. Yoshida *et al.*, *J. Biol. Chem.* **265(28)**: 17174-17179 (1990)) was incubated with 30 µg of the cloned recombinant hHDAC-1 for 10 minutes at 37 °C. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCl (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [<sup>3</sup>H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 °C for 30 minutes prior to initiation of the enzymatic assay. IC<sub>50</sub> values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition. IC<sub>50</sub> values for representative compounds are presented in the third column of Table 5.

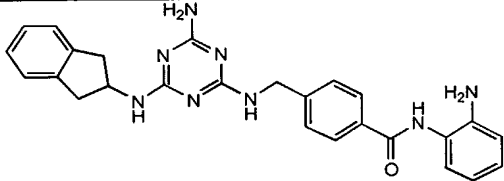
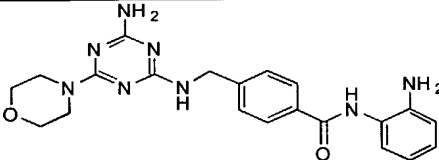
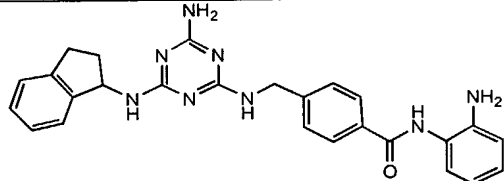
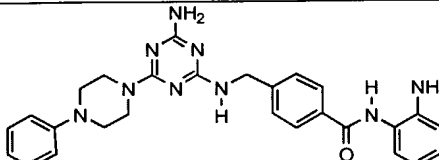
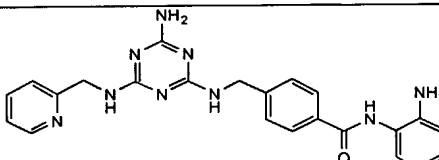
##### 2. MTT Assay

**[0395]** HCT116 cells (2000/well) were plated into 96-well tissue culture plates one day before compound treatment. Compounds at various concentrations were added to the cells. The cells were incubated for 72 hours at 37°C in 5% CO<sub>2</sub> incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before one volume of solubilization buffer (50% N,N-dimethylformamide, 20% SDS, pH 4.7) was added onto the cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM using an MR700 plate reader (Dynatech Laboratories Inc.). OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of that of solvent treated cells is determined as MTT IC<sub>50</sub>. IC<sub>50</sub> values for representative compounds are presented in the fourth column of Table 5.

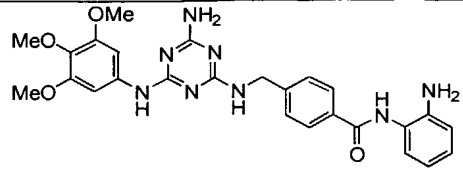
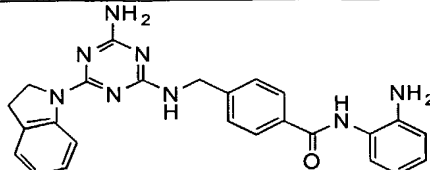
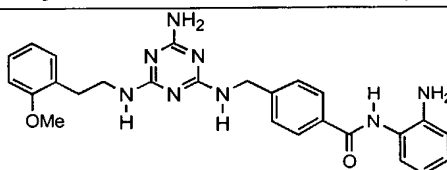
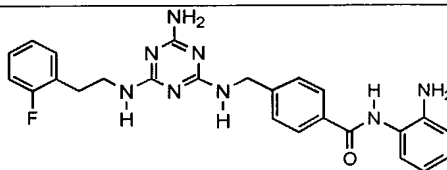
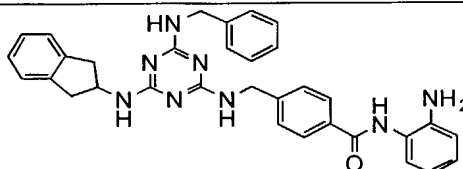
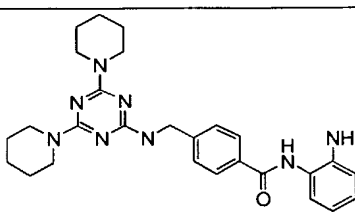
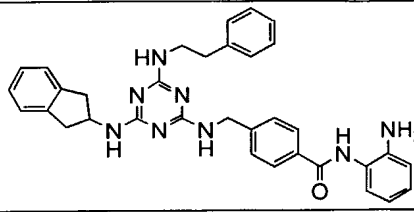
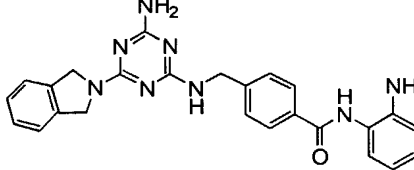
### 3. Histone H4 acetylation in whole cells by immunoblots

**[0396]** T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 h. Histones were extracted from the cells after the culture period as described by M. Yoshida *et al.* (*J. Biol. Chem.* **265**(28): 17174-17179 (1990)). 20 g of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry. Representative data are presented in the fifth column of Table 5. Data are presented as the concentration effective for reducing the acetylated H-4 signal by 50% (EC<sub>50</sub>).

**Table 5a: Inhibition of Histone Deacetylase**

| Cpd | Structure   | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|---|--|--|--|
| 8   |   | 0.4  | 0.5  | 1  |
| 9   |  | 2  | 0.7  | 5  |
| 10  |  | 2  | 0.6  | 1  |
| 11  |  | 2  | 0.6  | 2  |
| 12  |  | 2  | 2  | 5  |

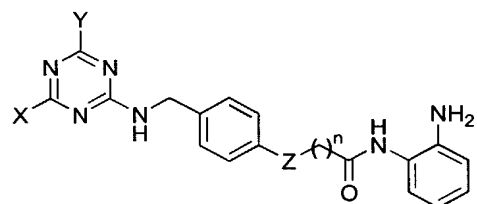
| Cpd | Structure | HumanHDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4Ac(T24)<br>EC <sub>50</sub> (μM) |
|-----|-----------|--------------------------------------|--------------------------------------|------------------------------------|
| 14  |           | 0.3                                  | 1                                    | 5                                  |
| 15  |           | 0.5                                  | 0.2                                  | 3                                  |
| 16  |           | 1                                    | 0.4                                  | 1                                  |
| 17  |           | 0.9                                  | 1                                    | 2                                  |
| 18  |           | 0.8                                  | 0.6                                  | 3                                  |
| 18b |           | 0.6                                  | 5                                    | 10                                 |
| 19  |           | 0.9                                  | 1                                    | 1                                  |
| 20  |           | 0.5                                  | 0.3                                  | 1                                  |

| Cpd | Structure   | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|---|--|--|--|
| 21  |    | 4  | 4  | 25                                       |
| 22  |    | 3  | 0.8  | 1  |
| 23  |    | 2  | 0.7  | 1  |
| 24  |   | 3  | 0.6  | 1  |
| 25  |  | 0.8  | 0.3  | 5  |
| 26  |  | 0.5  | 2  | na                                       |
| 27  |  | 0.4  | 2  | na                                       |
| 28  |  | 2  | 0.5  | 1  |

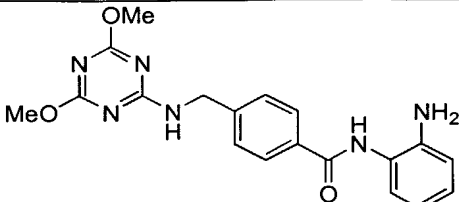
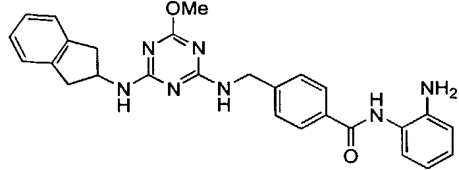
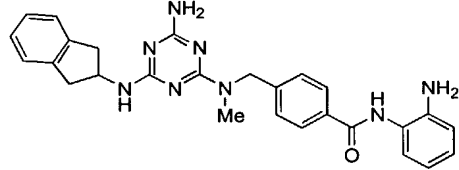
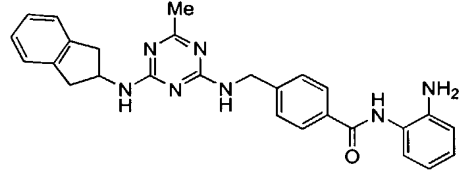
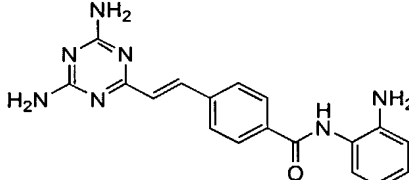
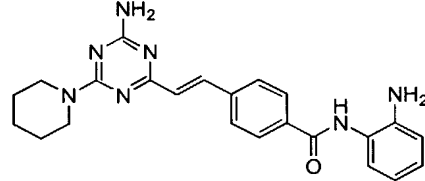
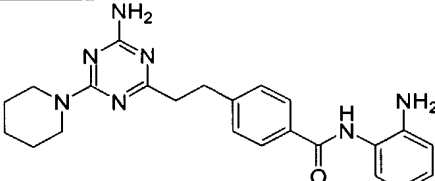
| Cpd | Structure | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----------|--|--|--|
| 29  |           | 2  | 2  | 1  |
| 30  |           | 1  | 3  | 1  |
| 83  |           | 3  | 5  | 5  |

(na = not available; 99 = >25  $\mu$ M)

Table 5b



| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----|-----------|---|--|--|
| 135 | 204 |           | 4   | na   | 5  |
| 136 | 207 |           | 0.4   | 0.6  | 2  |
| 137 | 210 |           | 3   | 0.9  | 1  |

| Ex   | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|------|-----|---|---|--|--|
| 138  | 212 |    | 3   | 1  | 1  |
| 139  | 214 |    | 3   | 0.9  | 1  |
| 140  | 216 |    | 0.5   | 0.4  | 2  |
| 141  | 218 |   | 0.1   | 0.5  | na                                       |
| 142  | 220 |  | 7   | 6  | na                                       |
| 143a | 223 |  | 11  | 2  | na                                       |
| 143b | 224 |  | 5   | 3  | na                                       |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4Ac(T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|--------------------------------------|------------------------------------|
| 329 | 470 |           | 2                                     | 0.7                                  | 3                                  |
| 330 | 471 |           | 0.4                                   | 1                                    | 3                                  |
| 331 | 472 |           | 3                                     | 1                                    | 1                                  |
| 332 | 473 |           | 4                                     | 3                                    | na                                 |
| 333 | 474 |           | 3                                     | 1                                    | 1                                  |
| 334 | 475 |           | 0.6                                   | 2                                    | na                                 |
| 335 | 476 |           | 2                                     | 1                                    | 2                                  |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4Ac(T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|--------------------------------------|------------------------------------|
| 336 | 477 |           | 1                                     | 0.7                                  | na                                 |
| 337 | 478 |           | 3                                     | 0.7                                  | na                                 |
| 338 | 479 |           | 0.4                                   | 0.6                                  | na                                 |
| 339 | 480 |           | 0.8                                   | 0.5                                  | na                                 |
| 340 | 481 |           | 6                                     | 0.7                                  | na                                 |
| 341 | 482 |           | 0.1                                   | 0.7                                  | na                                 |
| 342 | 483 |           | 4                                     | na                                   | na                                 |

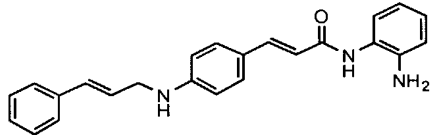
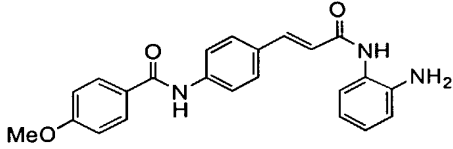
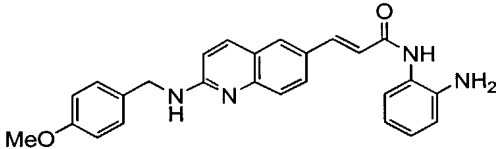
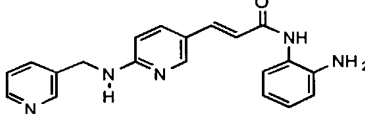
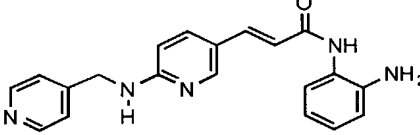
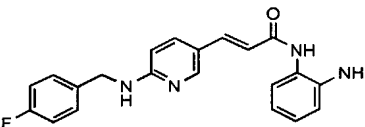
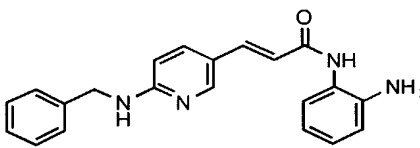
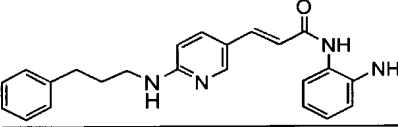
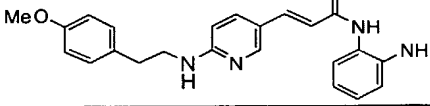


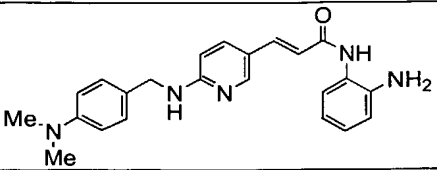
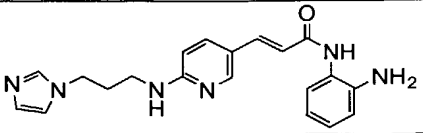
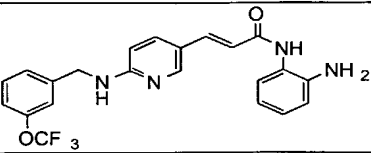
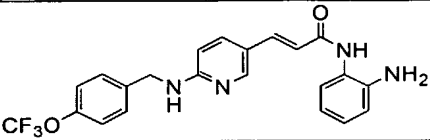
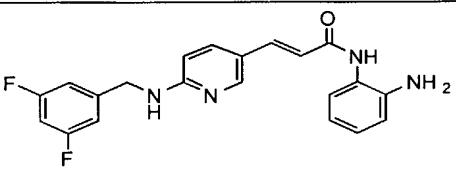
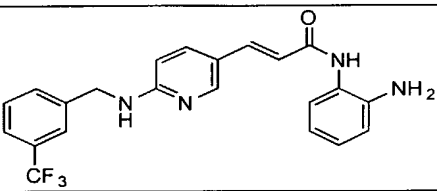
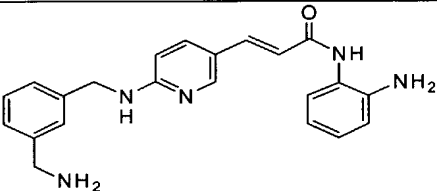
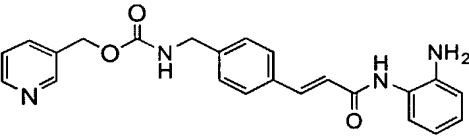
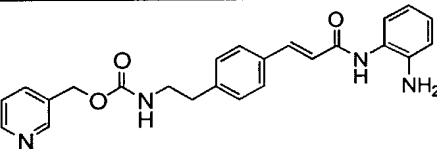
| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----|-----------|---|--|--|
| 343 | 484 |           | 2   | 0.3  | na                                       |
| 344 | 485 |           | 0.4   | 3  | na                                       |

(na=nonavailable)

Table 5c

| Cpd | Structure | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----------|--|--|--|
| 51  |           | 22   | 4  | na                                       |
| 55b |           | 3  | 8  | 3  |
| 59  |           | 12   | 22   | na                                       |
| 61b |           | 7  | 12   | na                                       |
| 65  |           | 4  | 37   | na                                       |

| Cpd | Structure   | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|---|--|--|--|
| 71  |    | 10   | 44   | na                                       |
| 72  |    | 16   | 21   | na                                       |
| 88  |    | na   | >39  | na                                       |
| 90  |    | 10   | 5  | 5  |
| 91  |   | 4  | 7  | 5  |
| 92  |  | 5  | 2  | 3  |
| 93  |  | 3  | 1  | 5  |
| 94  |  | 3  | 2  | 5  |
| 95  |  | 3  | 2  | 10                                       |

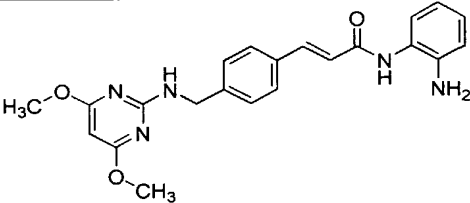
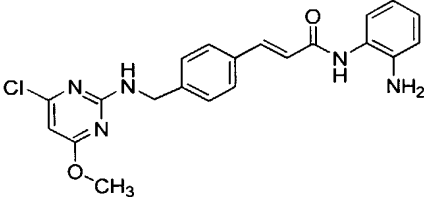
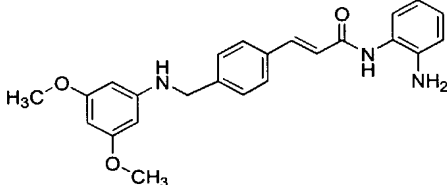
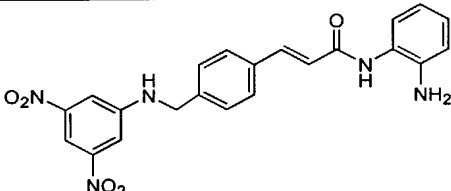
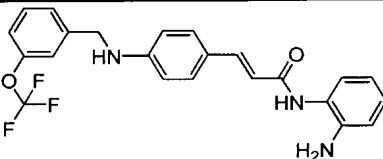
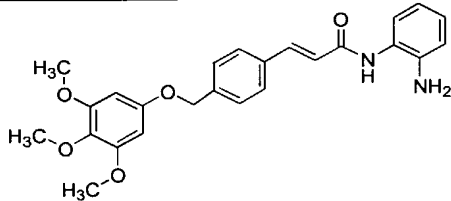
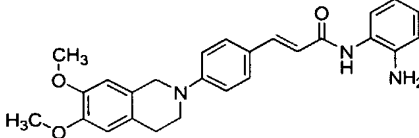
| Cpd | Structure   | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|---|--|--|--|
| 96  |    | 4  | 3  | 25                                       |
| 97  |    | 10   | 12   | na                                       |
| 98  |    | 0.4  | 2  | 15                                       |
| 99  |    | 2  | 5  | 10                                       |
| 100 |   | 4  | 3  | 5  |
| 101 |  | 3  | 0.9  | 5  |
| 102 |  | 20   | 6  | na                                       |
| 104 |  | 10   | 9  | 5  |
| 105 |  | 16   | 14   | na                                       |

| Cpd | Structure | HumanHDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4Ac(T24)<br>EC <sub>50</sub> (μM) |
|-----|-----------|--------------------------------------|--------------------------------------|------------------------------------|
| 106 |           | 2                                    | 2                                    | 1                                  |
| 107 |           | 15                                   | 17                                   | na                                 |
| 108 |           | 3                                    | 5                                    | 5                                  |
| 109 |           | 5                                    | 8                                    | 15                                 |
| 110 |           | 3                                    | 999                                  | na                                 |
| 111 |           | 10                                   | 2                                    | 99                                 |
| 112 |           | 2                                    | 5                                    | 5                                  |
| 113 |           |                                      | 0.3                                  | 5                                  |

| Cpd | Structure | HumanHDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----------|--|--|--|
| 114 |           | 25   | 0.5  | 99                                       |
| 115 |           | 15   | 9  | na                                       |
| 116 |           | 4  | 2  | 5  |
| 117 |           | 7  | 3  | na                                       |
| 118 |           | 11   | 8  | na                                       |

Table 5d

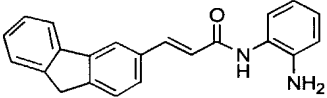
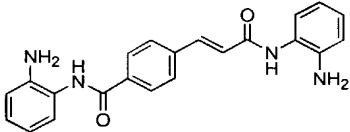
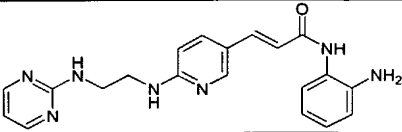
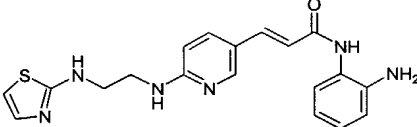
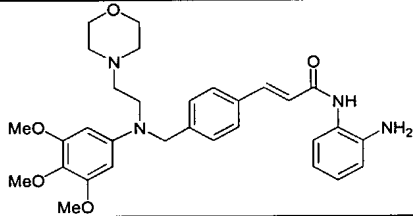
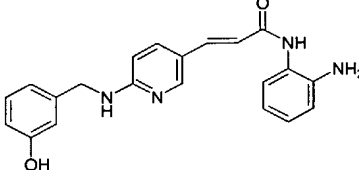
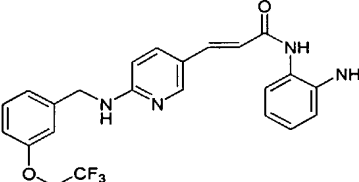
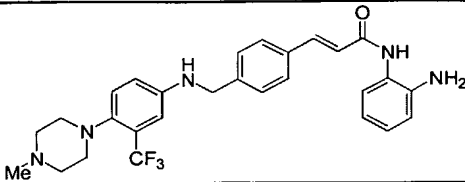
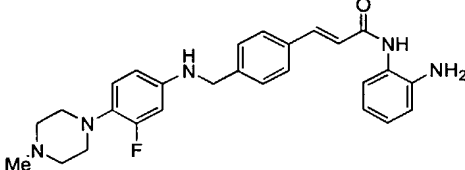
| Ex. | Cpd | Structure | HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----|-----------|---------------------------------------|--|--|
| 338 | 481 |           | 22                                    | 10   | -  |
| 339 | 484 |           | 20                                    | 12   | -  |

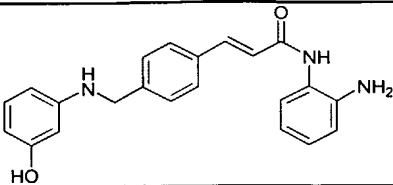
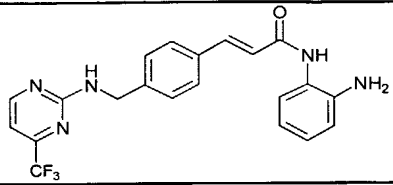
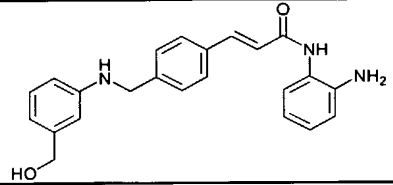
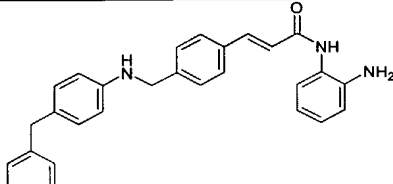
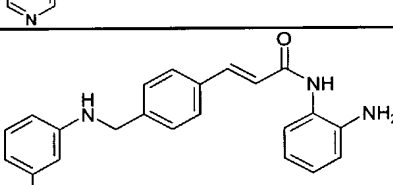
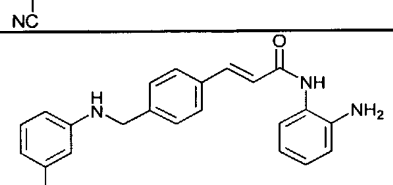
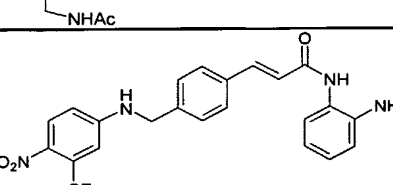
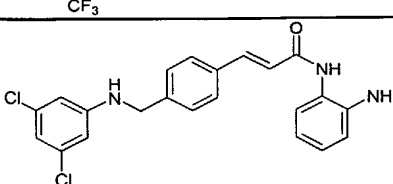
| Ex. | Cpd | Structure   | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|---|--------------------------|-------------------------------|-----------------------------|
| 347 | 492 |    | 4                        | 9                             | 10                          |
| 348 | 493 |    | 4                        | 5                             | -                           |
| 349 | 494 |    | 3                        | 4                             | -                           |
| 350 | 495 |   | 4                        | 7                             | -                           |
| 351 | 496 |  | 8                        | 13                            | -                           |
| 352 | 497 |  | 15                       | 6                             | -                           |
| 353 | 498 |  | >25                      | -                             | -                           |

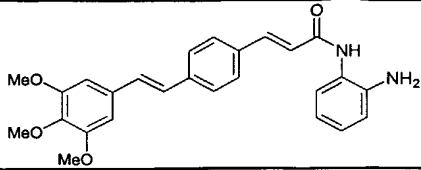
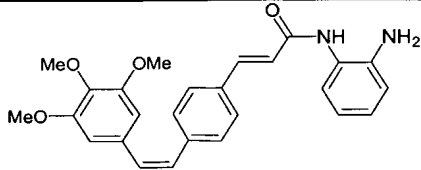
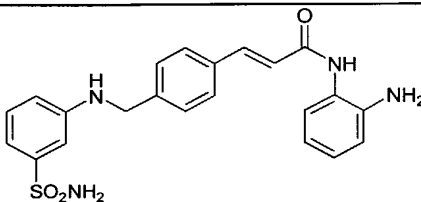
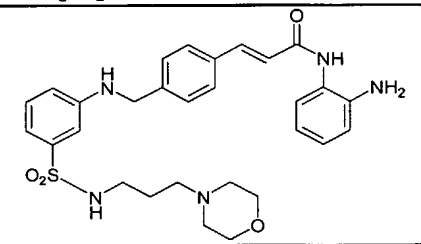
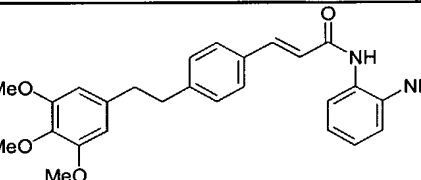
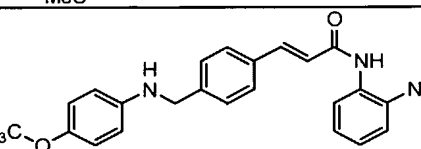
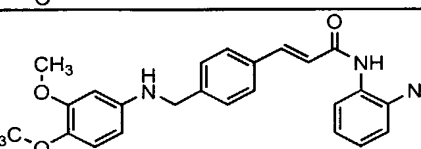
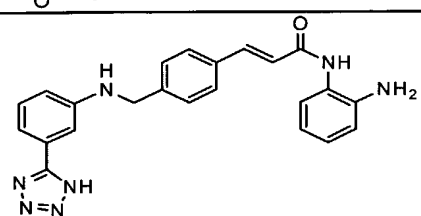
| Ex. | Cpd | Structure | HDAC-1<br>IC50(μM) | MTT(HCT116)<br>IC50(μM) | H4Ac(T24)<br>EC50(μM) |
|-----|-----|-----------|--------------------|-------------------------|-----------------------|
| 354 | 499 |           | >25                | 2                       | >25                   |
| 355 | 500 |           | 23                 | 37                      | -                     |
| 356 | 501 |           | 4                  | 10                      | -                     |
| 357 | 502 |           | 3                  | >25                     | -                     |
| 358 | 503 |           | 5                  | >25                     | -                     |
| 359 | 504 |           | 5                  | >25                     | -                     |
| 360 | 505 |           | 3                  | 6                       | -                     |
| 361 | 506 |           | 15                 | 11                      | -                     |

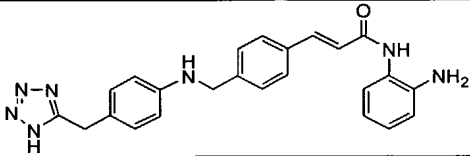
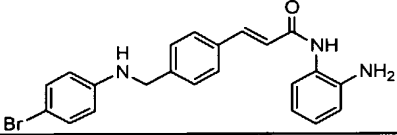
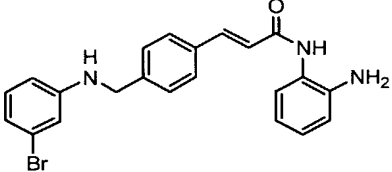
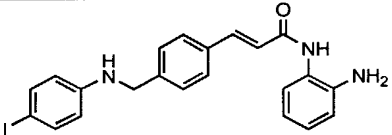
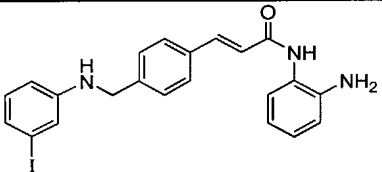
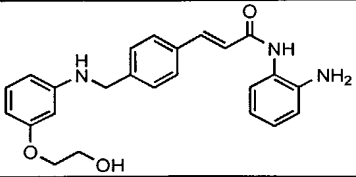
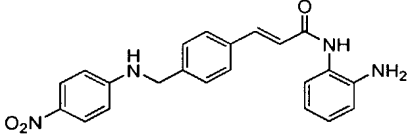
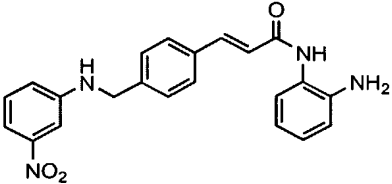
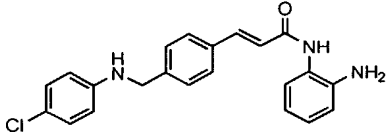
| Ex. | Cpd | Structure | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|-----------|--------------------------|-------------------------------|-----------------------------|
| 362 | 507 |           | 17                       | 10                            | -                           |
| 363 | 508 |           | 22                       | 11                            | -                           |
| 364 | 509 |           | 17                       | 11                            | -                           |
| 365 | 510 |           | 6                        | 5                             | -                           |
| 366 | 511 |           | 4                        | >25                           | -                           |
| 367 | 512 |           | 3                        | 3                             | 5                           |
| 371 | 516 |           | 15                       | 15                            | -                           |
| 372 | 517 |           | 6                        | 5                             | -                           |
| 373 | 518 |           | 4                        | 2                             | 5                           |



| Ex. | Cpd | Structure   | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|---|--------------------------|-------------------------------|-----------------------------|
| 374 | 519 |    | 99                       | 6                             | -                           |
| 375 | 520 |    | 5                        | 3                             | -                           |
| 376 | 521 |    | 5                        | 2                             | 10                          |
| 377 | 522 |    | 17                       | 30                            | -                           |
| 378 | 523 |   | 8                        | 6                             | 10                          |
| 379 | 524 |  | 3                        | 2                             | 3                           |
| 380 | 525 |  | 3                        | 4                             | 5                           |
| 381 | 526 |  | 2                        | 0.8                           | 1                           |
| 382 | 527 |  | 4                        | 3                             | -                           |

| Ex. | Cpd | Structure   | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|---|--------------------------|-------------------------------|-----------------------------|
| 383 | 528 |    | 20                       | 32                            | -                           |
| 384 | 529 |    | 5                        | 17                            | -                           |
| 385 | 530 |    | 8                        | 9                             | -                           |
| 386 | 531 |   | 3                        | 2                             | 20                          |
| 387 | 532 |  | 3                        | 5                             | -                           |
| 388 | 533 |  | 5                        | 11                            | -                           |
| 389 | 534 |  | 3                        | 5                             | -                           |
| 390 | 535 |  | 4                        | 6                             | -                           |

| Ex. | Cpd | Structure   | HDAC-1<br>IC50(μM) | MTT(HCT116)<br>IC50(μM) | H4Ac(T24)<br>EC50(μM) |
|-----|-----|---|--------------------|-------------------------|-----------------------|
| 391 | 536 |    | 18                 | 9                       | -                     |
| 392 | 537 |    | 11                 | 2                       | >25                   |
| 393 | 538 |    | 4                  | 12                      | -                     |
| 394 | 539 |   | 2                  | 10                      | -                     |
| 395 | 540 |  | 10                 | 10                      | -                     |
| 396 | 541 |  | 4                  | 12                      | -                     |
| 397 | 542 |  | 2                  | 5                       | 4                     |
| 398 | 543 |  | 15                 | >25                     | -                     |

| Ex. | Cpd | Structure   | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|---|--------------------------|-------------------------------|-----------------------------|
| 399 | 544 |    | 17                       | 45                            | -                           |
| 400 | 545 |    | 2                        | 12                            | -                           |
| 401 | 546 |    | 3                        | 10                            | -                           |
| 402 | 547 |    | 4                        | 8                             | -                           |
| 403 | 548 |   | 3                        | 9                             | -                           |
| 404 | 549 |  | 4                        | 19                            | -                           |
| 405 | 550 |  | 4                        | 15                            | -                           |
| 406 | 551 |  | 24                       | 9                             | -                           |
| 407 | 552 |  | 4                        | 22                            | -                           |

| Ex. | Cpd | Structure | HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----|-----------|---------------------------------------|--|--|
| 408 | 553 |           | 4                                     | 12   | -  |
| 409 | 554 |           | 15                                    | 12   | -  |
| 410 | 555 |           | 14                                    | 7  | -  |
| 411 | 556 |           | 1                                     | 0.4  | 15                                       |
| 412 | 557 |           | 4                                     | 6  | -  |
| 413 | 558 |           | 7                                     | 10   | -  |
| 414 | 559 |           | 4                                     | 11   | -  |
| 415 | 560 |           | 21                                    | 6  | -  |
| 416 | 561 |           | >25                                   | >25  | -  |

| Ex. | Cpd | Structure | HDAC-1<br>IC50( $\mu$ M) | MTT(HCT116)<br>IC50( $\mu$ M) | H4Ac(T24)<br>EC50( $\mu$ M) |
|-----|-----|-----------|--------------------------|-------------------------------|-----------------------------|
| 417 | 562 |           | 5                        | 5                             | -                           |
| 418 | 563 |           | 24                       | 6                             | -                           |
| 419 | 564 |           | >25                      | >25                           | -                           |
| 420 | 565 |           | 5                        | 17                            | -                           |
| 421 | 566 |           | 3                        | 16                            | -                           |
| 422 | 567 |           | 13                       | 3                             | -                           |
| 423 | 568 |           | >25                      | 39                            | -                           |
| 424 | 569 |           | 18                       | 6                             | -                           |

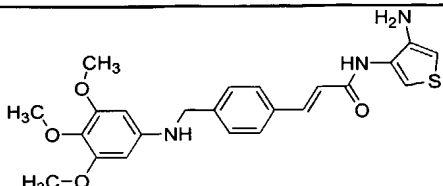
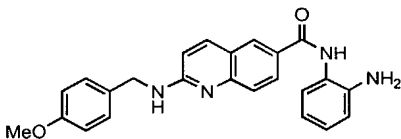
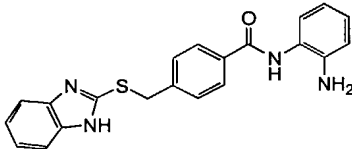
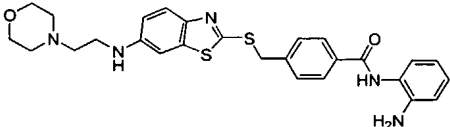
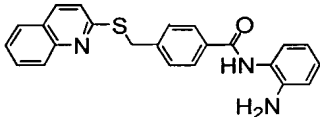
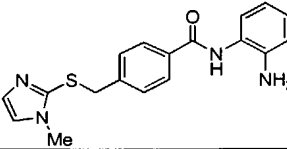
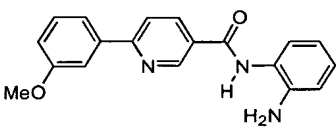
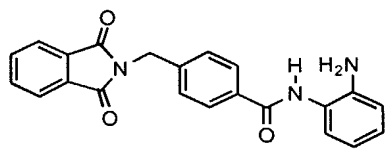
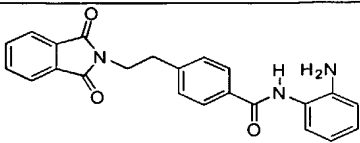
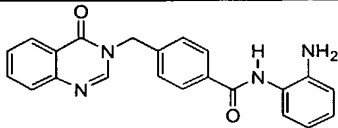
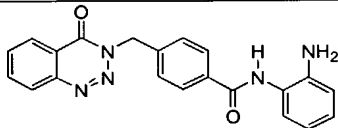
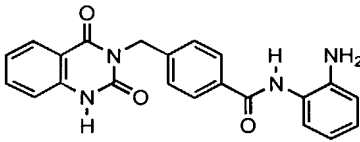
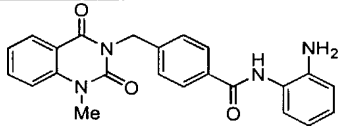
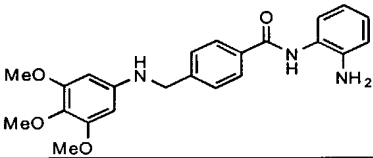
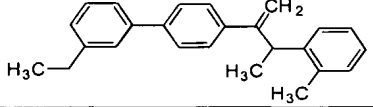
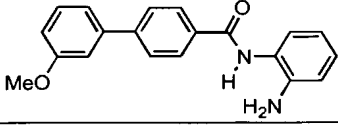
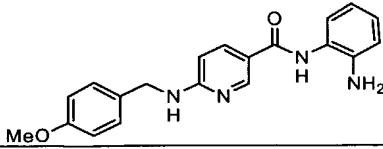
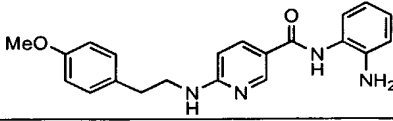
| Ex. | Cpd | Structure   | HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4Ac(T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|-----|---|---------------------------------------|--|--|
| 425 | 570 |  | 6                                     | 0.6  | 2  |

Table 5e

| Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> ( $\mu$ M) | MTT(HCT116)<br>IC <sub>50</sub> ( $\mu$ M) | H4 Ac (T24)<br>EC <sub>50</sub> ( $\mu$ M) |
|-----|---|---|--|--|
| 87  |    | 2   | 1  | 5  |
| 126 |   | 0.3   | 0.2  | 1  |
| 128 |  | 1   | 0.3  | 5  |
| 131 |  | 0.3   | 0.9  | 2  |
| 139 |  | 3   | 3  | 5  |
| 141 |  | 7   | 10   | na   |
| 149 |  | 1   | 5  | 5  |

| Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|---|---------------------------------------|--------------------------------------|--------------------------------------|
| 152 |    | 0.3                                   | 11                                   | na                                   |
| 154 |    | 0.3                                   | 0.4                                  | <1                                   |
| 155 |    | 0.4                                   | 0.4                                  | 1                                    |
| 157 |    | 2                                     | 0.6                                  | 1                                    |
| 158 |   | 0.4                                   | 0.2                                  | 1                                    |
| 164 |  | 3                                     | 2                                    | 3                                    |
| 165 |  | 9                                     | 4                                    | 25                                   |
| 166 |  | 2                                     | 5                                    | 5                                    |
| 167 |  | 4                                     | 0.5                                  | 2                                    |
| 168 |  | 3                                     | 0.8                                  | 2                                    |



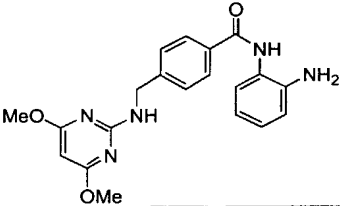
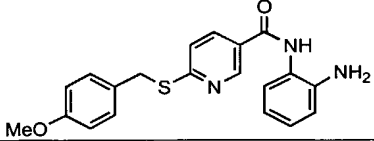
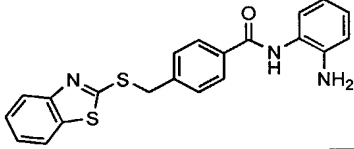
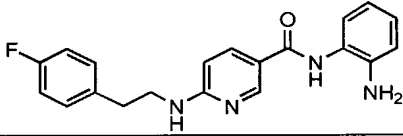
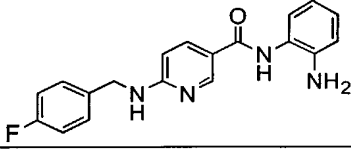
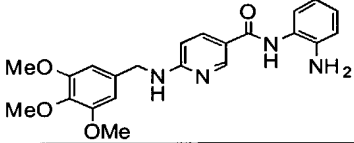
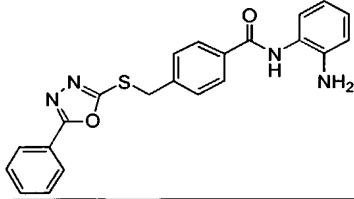
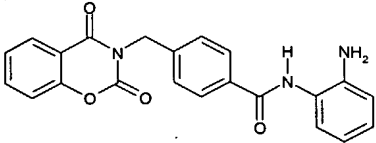
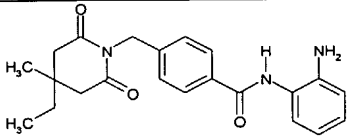
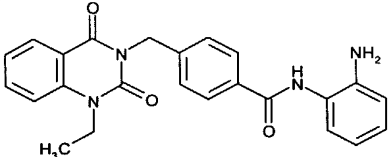
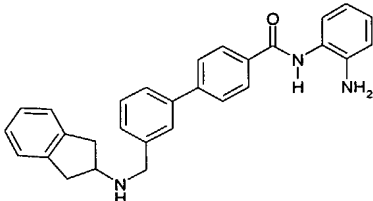
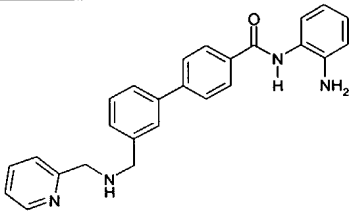
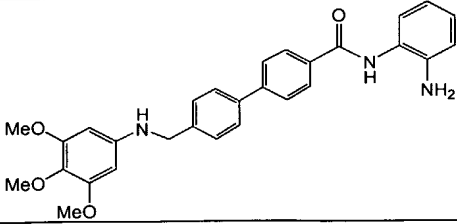
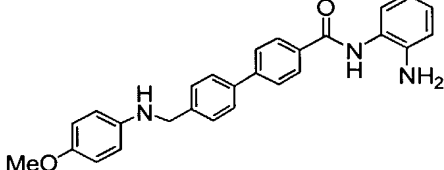
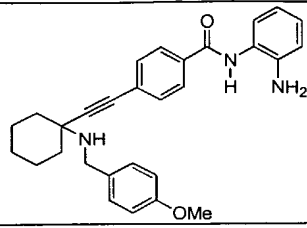
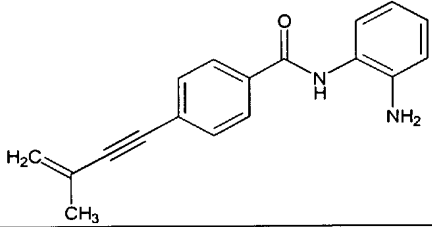
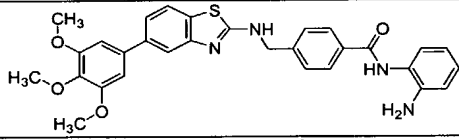
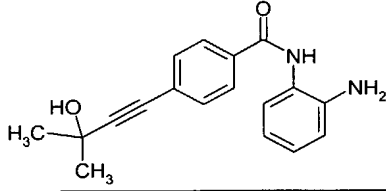
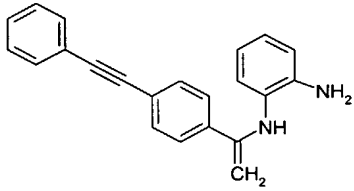
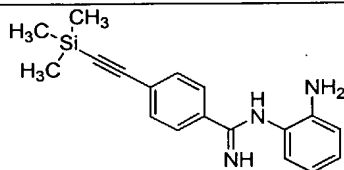
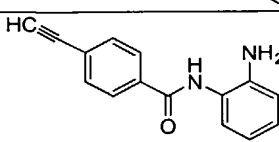
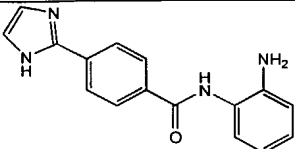
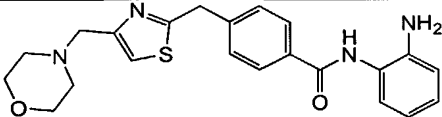
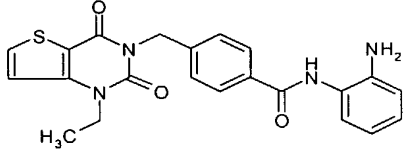
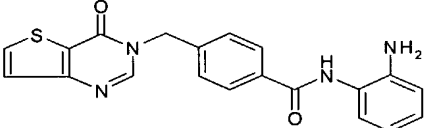
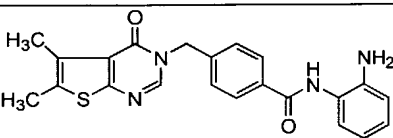
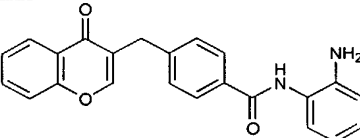
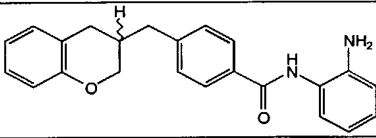
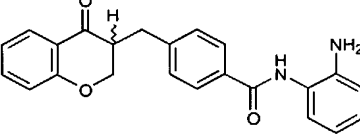
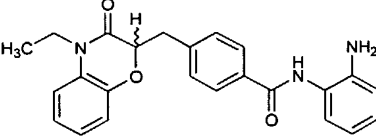
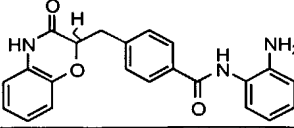
| Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT(HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|---|---------------------------------------|--------------------------------------|--------------------------------------|
| 169 |    | 0.3                                   | 0.7                                  | 1                                    |
| 171 |    | 8                                     | 3                                    | 25                                   |
| 172 |    | 0.4                                   | 1                                    | 3                                    |
| 174 |    | 4                                     | 0.4                                  | 5                                    |
| 175 |   | 4                                     | 0.5                                  | 3                                    |
| 176 |  | 5                                     | 1                                    | 3                                    |
| 177 |  | 1                                     | 0.4                                  | 1                                    |

Table 5f

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 117 | 179 |    | 1                                     | 0.3                                   | 1                                    |
| 118 | 180 |    | 3                                     | 2                                     | 5                                    |
| 119 | 181 |    | 0.5                                   | 0.4                                   | 1                                    |
| 122 | 186 |   | 2                                     | 2                                     | 2                                    |
| 123 | 187 |  | 2                                     | 5                                     | 2                                    |
| 125 | 189 |  | 3                                     | 2                                     | 5                                    |
| 126 | 190 |  | 3                                     | 1                                     | >5                                   |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 127 | 192 |    | 2                                     | 1                                     | 3                                    |
| 128 | 193 |    | 4                                     | 16                                    |                                      |
| 129 | 194 |    | 3                                     | 11                                    |                                      |
| 130 | 195 |   | 7                                     | 9                                     |                                      |
| 131 | 196 |  | 4                                     | 3                                     |                                      |
| 132 | 198 |  | 24                                    | 14                                    |                                      |
| 133 | 199 |  | 7                                     | 9                                     |                                      |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 134 | 201 |           | 11                                    | 5                                     |                                      |
| 144 | 228 |           | 3                                     | 0.3                                   | 1                                    |
| 145 | 231 |           | 4                                     | 1                                     | 3                                    |
| 146 | 233 |           | 0.9                                   | 0.3                                   | 1                                    |
| 147 | 236 |           | 5                                     | 6                                     |                                      |
| 148 | 238 |           | 3                                     | 6                                     |                                      |
| 149 | 240 |           | 1.8                                   | 10                                    |                                      |
| 150 | 243 |           | 2                                     | 0.8                                   | 1                                    |
| 151 | 247 |           | 3                                     | 0.6                                   | 2                                    |

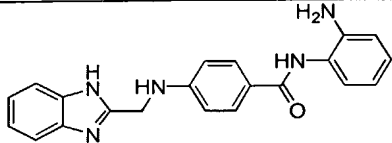
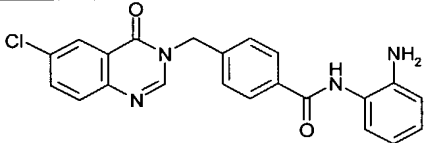
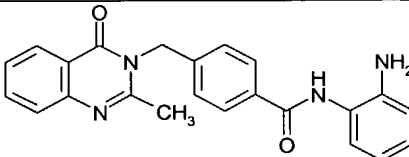
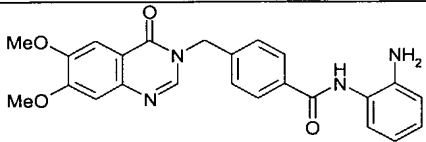
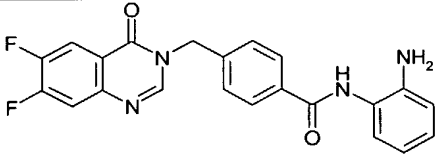
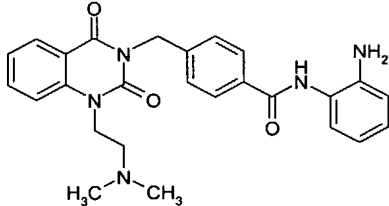
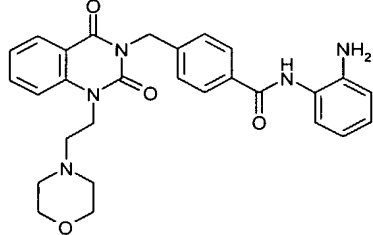
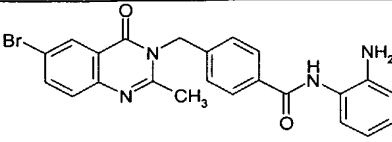
| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 152 | 249 |    | 4                                     | 1                                     | 2                                    |
| 153 | 252 |    | 8                                     | 1                                     | 2                                    |
| 154 | 255 |    | 2                                     | 0.8                                   | 1                                    |
| 155 | 257 |    | 0.4                                   | 0.4                                   | 1                                    |
| 156 | 259 |   | 3                                     | 0.3                                   | 1                                    |
| 157 | 262 |  | 0.5                                   | 0.3                                   | 1                                    |
| 158 | 265 |  | 2                                     | 2                                     | 3                                    |
| 159 | 266 |  | 0.4                                   | 0.9                                   | 2                                    |
| 160 | 269 |  | 9                                     | 4                                     |                                      |
| 161 | 270 |  | 4                                     | 1                                     | 5                                    |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 162 | 272 |           | 2                                     | 0.6                                   | <1                                   |
| 163 | 275 |           | 4                                     | 0.9                                   | 2                                    |
| 164 | 277 |           | 4                                     | 0.3                                   | 1                                    |
| 165 | 281 |           | 0.5                                   | 0.6                                   | 1                                    |
| 166 | 284 |           | 3                                     | 5                                     |                                      |
| 167 | 286 |           | 5                                     | 2                                     |                                      |
| 168 | 289 |           | 17                                    | 5                                     |                                      |
| 169 | 290 |           | 11                                    | 3                                     |                                      |
| 170 | 296 |           | 20                                    | 7                                     |                                      |
| 171 | 297 |           | 7                                     | 0.4                                   | 1                                    |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 172 | 301 |           | 3                                     | 3                                     |                                      |
| 173 | 305 |           | 4                                     | 2                                     |                                      |
| 174 | 311 |           | 0.9                                   | 0.7                                   | 1                                    |
| 178 | 317 |           | 2                                     | 0.3                                   | 1                                    |
| 179 | 319 |           | 4                                     | 8                                     |                                      |
| 180 | 320 |           | 2                                     |                                       | 1                                    |
| 181 | 321 |           | 0.5                                   | 0.3                                   | 5                                    |
| 182 | 322 |           | 0.7                                   | 0.4                                   | 2                                    |
| 183 | 323 |           | 1                                     | 0.6                                   | 1                                    |

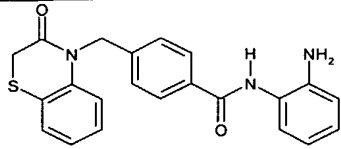
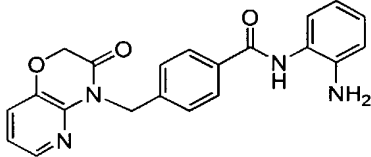
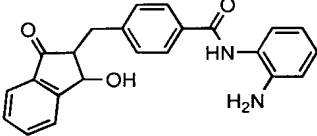
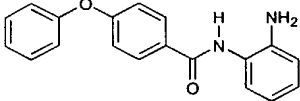
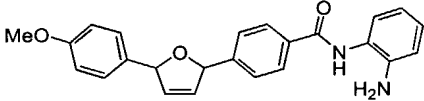
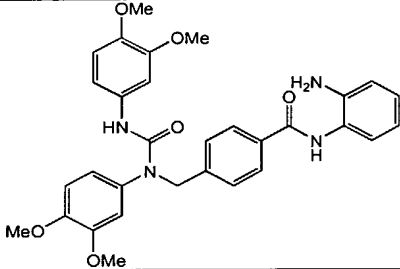
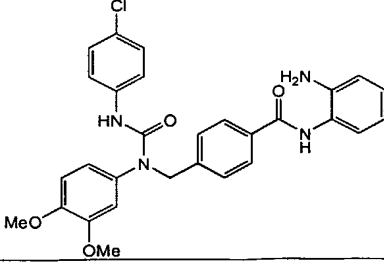
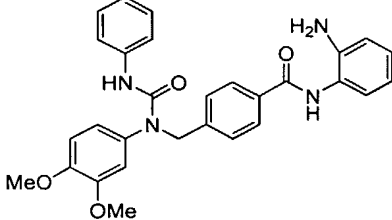
| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 184 | 325 |           | 0.3                                   | 1                                     | 2                                    |
| 185 | 326 |           | 1                                     | 1                                     | 3                                    |
| 186 | 327 |           | 2                                     | 5                                     | 3                                    |
| 187 | 328 |           | 17                                    | 10                                    |                                      |
| 189 | 330 |           | 3                                     | 2                                     | 1                                    |
| 190 | 331 |           | 4                                     | 10                                    |                                      |
| 191 | 332 |           | 0.4                                   | 1                                     | 5                                    |
| 192 | 333 |           | 2                                     | 0.1                                   | 1                                    |

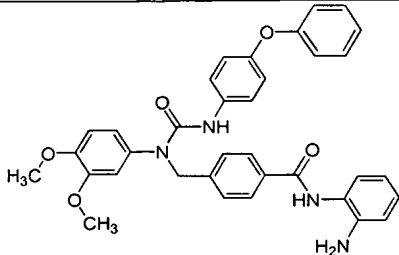
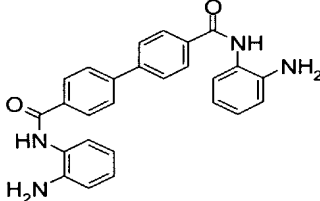
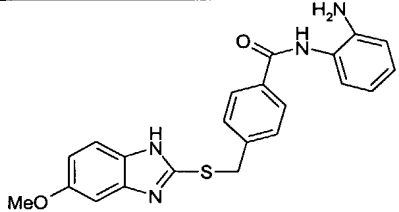
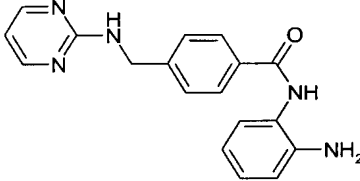
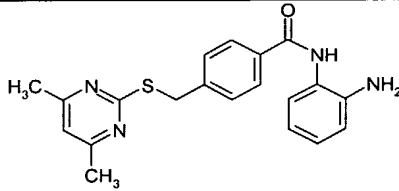
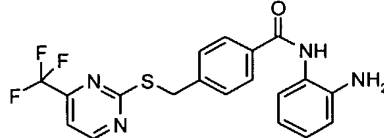
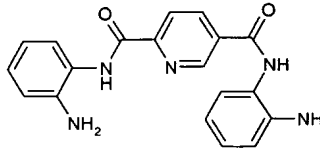


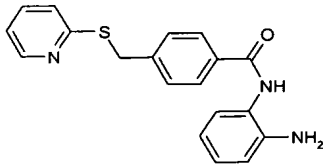
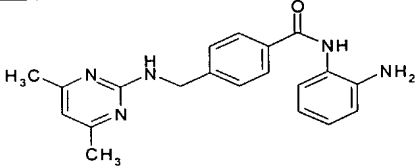
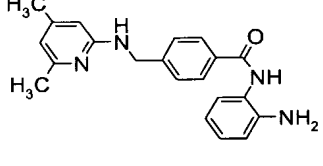
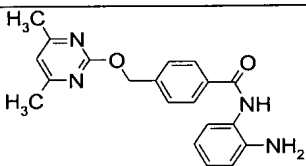
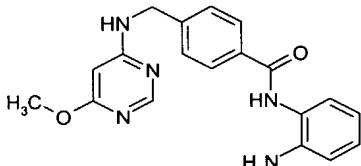
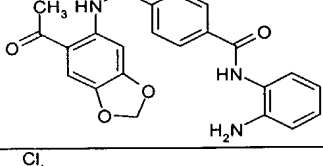
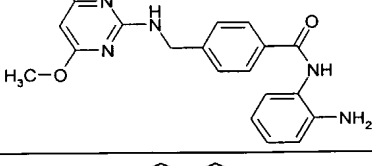
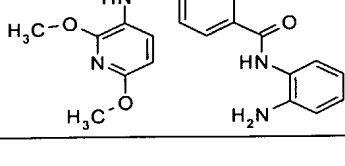
| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 193 | 334 |    | 8                                     | 0.2                                   | 1                                    |
| 195 | 336 |    | 1                                     | 0.4                                   | <1                                   |
| 196 | 337 |    | 3                                     | 0.6                                   | 1                                    |
| 197 | 338 |    | 2                                     | 0.5                                   | 3                                    |
| 198 | 339 |   | 4                                     | 3                                     |                                      |
| 199 | 340 |  | 2                                     | 1                                     | 1                                    |
| 200 | 341 |  | 4                                     | 1                                     | 3                                    |
| 201 | 342 |  | 3                                     | 0.4                                   | 1                                    |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 202 | 343 |           | 0.5                                   | 0.3                                   | 1                                    |
| 203 | 344 |           | 0.5                                   | 0.2                                   | 1                                    |
| 204 | 345 |           | 0.4                                   | 0.8                                   | 1                                    |
| 205 | 346 |           | 3                                     | 0.5                                   | <1                                   |
| 206 | 347 |           | 2                                     | 0.6                                   | 2                                    |
| 207 | 348 |           | 2                                     | 0.3                                   | 1                                    |
| 208 | 349 |           | 13                                    | 1                                     | 3                                    |
| 209 | 350 |           | 2                                     | 1                                     | 5                                    |
| 211 | 352 |           | 16                                    | 9                                     |                                      |

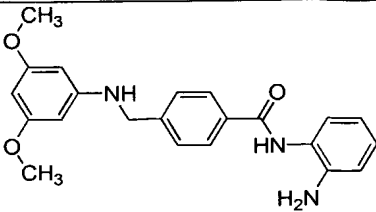
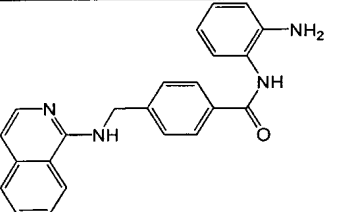
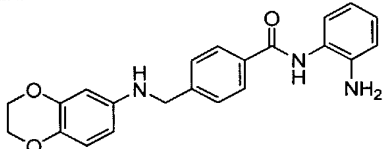
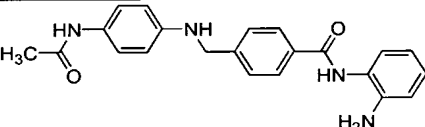
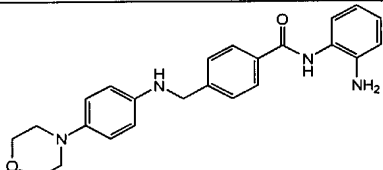
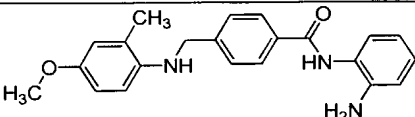
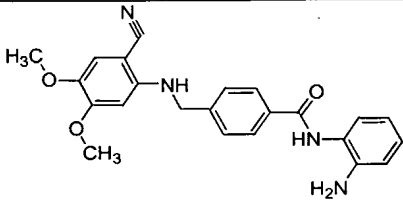
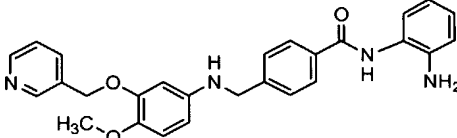
| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 212 | 353 |           | 3                                     | 10                                    |                                      |
| 213 | 354 |           | 15                                    | 5                                     |                                      |
| 214 | 355 |           | 25                                    | 10                                    |                                      |
| 215 | 356 |           | 5                                     | 2                                     |                                      |
| 216 | 357 |           | 4                                     | 0.4                                   | 2                                    |
| 217 | 358 |           | 3                                     | 1                                     | 2                                    |
| 218 | 359 |           | 2                                     | 0.3                                   | 1                                    |
| 219 | 360 |           | 5                                     | 0.2                                   | 1                                    |
| 220 | 361 |           | 2                                     | 0.5                                   | 1                                    |
| 221 | 362 |           | 2                                     | 0.7                                   | 1                                    |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 222 | 363 |    | 1                                     | 0.3                                   | 3                                    |
| 223 | 364 |    | 4                                     | 0.6                                   |                                      |
| 224 | 365 |    | 3                                     | 0.6                                   | 3                                    |
| 225 | 366 |    | 14                                    | 10                                    |                                      |
| 226 | 367 |   | 6                                     | 2                                     | 5                                    |
| 230 | 371 |  | 4                                     | 0.5                                   | 2                                    |
| 231 | 372 |  | 2                                     | 0.2                                   | 1                                    |
| 232 | 373 |  | 4                                     | 0.4                                   | 1                                    |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 233 | 374 |    | 2.5                                   | 0.3                                   | 1                                    |
| 234 | 375 |    | 3                                     | 4                                     | 25                                   |
| 235 | 376 |   | 3                                     | 0.1                                   | 1                                    |
| 236 | 377 |  | 4                                     | 2                                     | 3                                    |
| 237 | 378 |  | 2                                     | 0.7                                   | 2                                    |
| 238 | 379 |  | 2                                     | 0.6                                   | 15                                   |
| 239 | 380 |  | 6                                     | 8                                     |                                      |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 240 | 381 |    | 2                                     | 1                                     | 2                                    |
| 241 | 382 |    | 3                                     | 1                                     | 3                                    |
| 242 | 383 |    | 2                                     | 0.5                                   | 2                                    |
| 243 | 384 |   | 3                                     | 2                                     | 5                                    |
| 244 | 385 |  | 3                                     | 1                                     | 2                                    |
| 245 | 386 |  | 3                                     | 1                                     | 1                                    |
| 246 | 387 |  | 2                                     | 1                                     | 1                                    |
| 247 | 388 |  | 3                                     | 0.4                                   | 5                                    |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 248 | 389 |           | 3                                     | 0.2                                   | 1                                    |
| 249 | 390 |           | 2                                     | 0.8                                   | 5                                    |
| 250 | 391 |           | 1                                     | 0.9                                   | 3                                    |
| 251 | 392 |           | 4                                     | 1                                     | 1                                    |
| 252 | 393 |           | 4                                     | 0.6                                   | 1                                    |
| 253 | 394 |           | 4                                     | 2                                     | 25                                   |
| 254 | 395 |           | 2                                     | 1                                     | 5                                    |
| 255 | 396 |           | 2                                     | 0.7                                   | 5                                    |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 256 | 397 |    | 1                                     | 0.6                                   | 4                                    |
| 258 | 399 |    | 14                                    | 9                                     |                                      |
| 259 | 400 |    | 8                                     | 0.3                                   | 2                                    |
| 260 | 401 |   | 6                                     | 0.3                                   | 2                                    |
| 261 | 402 |  | 14                                    | 0.4                                   | 1                                    |
| 262 | 403 |  | 1                                     | 0.2                                   | 1                                    |
| 263 | 404 |  | 3                                     | 0.6                                   | 5                                    |
| 264 | 405 |  | 5                                     | 1                                     | 5                                    |

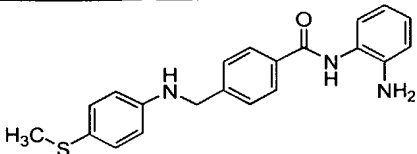
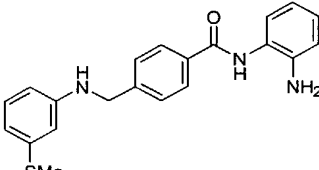
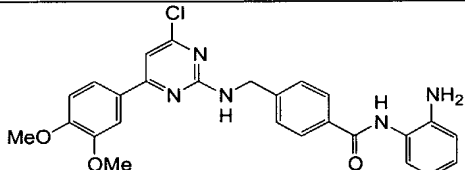
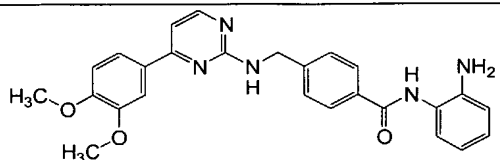
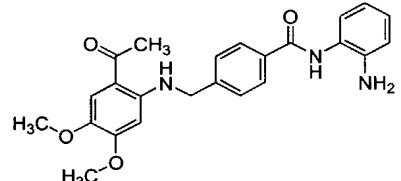
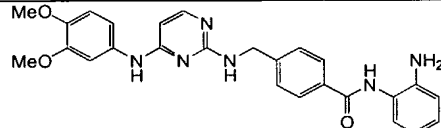
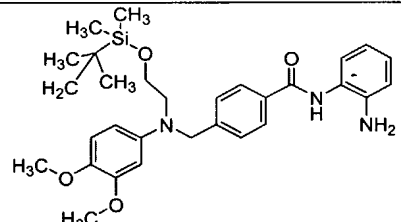
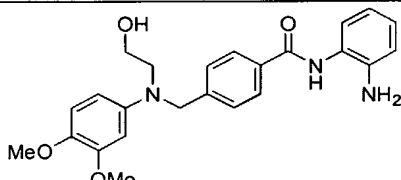


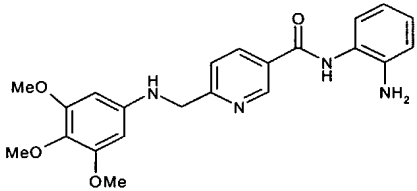
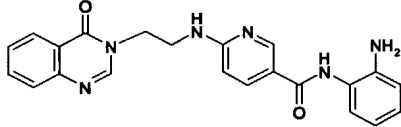
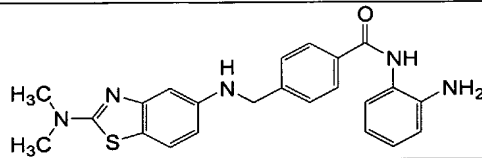
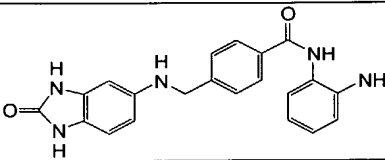
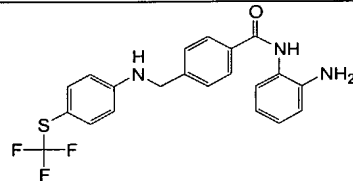
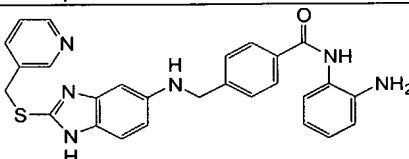
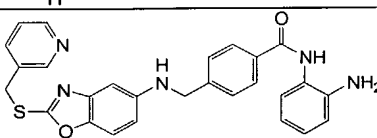
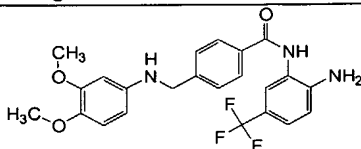
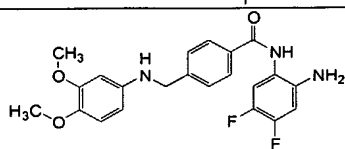
| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 265 | 406 |           | 3                                     | 11                                    |                                      |
| 266 | 407 |           | 3                                     | 2                                     |                                      |
| 267 | 408 |           | 4                                     | 2                                     |                                      |
| 268 | 409 |           | 3                                     | 1                                     | 9999                                 |
| 269 | 410 |           | 0.9                                   | 0.1                                   | >5                                   |
| 270 | 411 |           | 2                                     |                                       | 1                                    |
| 271 | 412 |           | 3                                     | 2                                     | 3                                    |
| 272 | 413 |           | 2                                     | 2                                     | 3                                    |

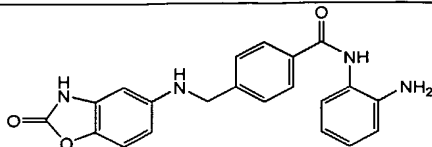
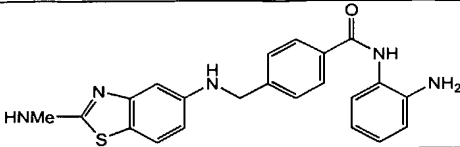
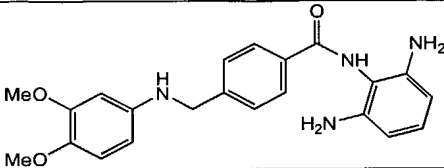
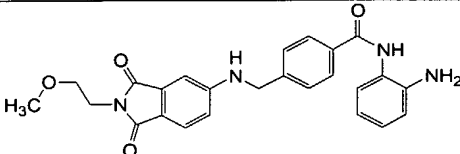
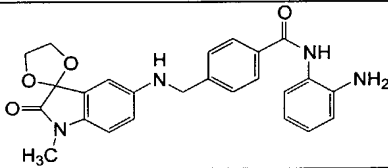
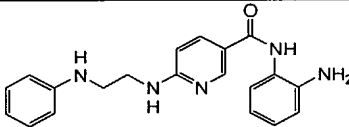
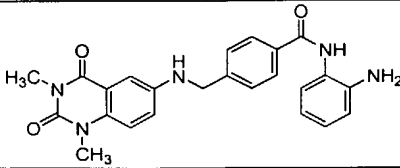
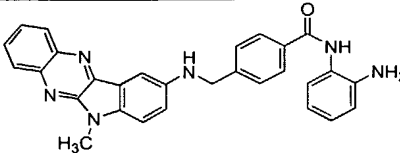
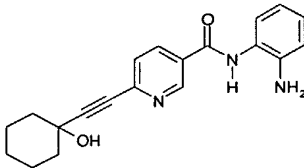
| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 273 | 414 |           | 3                                     | 1                                     | 1                                    |
| 274 | 415 |           | 3                                     | 1                                     | 3                                    |
| 275 | 416 |           | 3                                     | 0.6                                   | 1                                    |
| 276 | 417 |           | 3                                     | 1                                     | 1                                    |
| 277 | 418 |           | 3                                     | 0.9                                   | 2                                    |
| 278 | 419 |           | 2                                     | 1                                     | 5                                    |
| 279 | 420 |           | 3                                     | 0.7                                   | 1                                    |
| 280 | 421 |           | 4                                     | 0.6                                   | 1                                    |

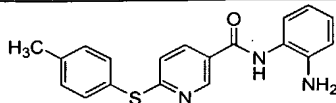
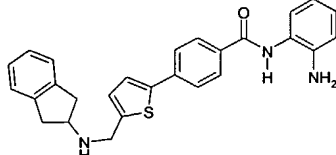
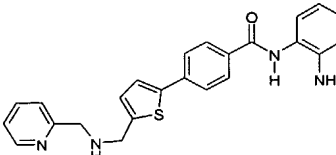
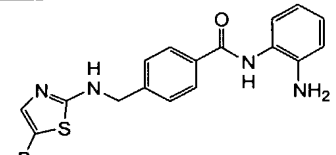
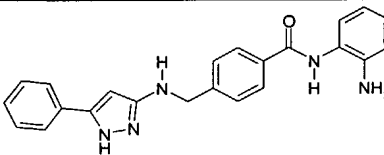
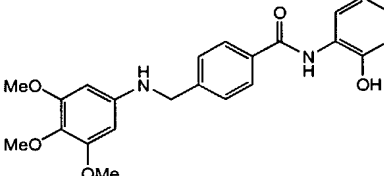
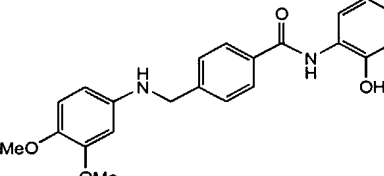
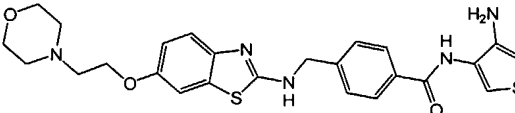
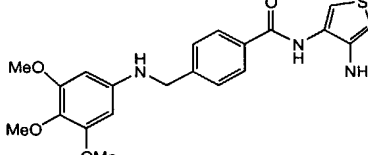
| Ex   | Cpd  | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|------|------|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 281  | 422  |           | <0.05                                 | 0.9                                   | 5                                    |
| 282  | 423  |           | 0.5                                   | 1                                     | 3                                    |
| 283a | 424b |           | 2                                     | 0.4                                   | 1                                    |
| 283b | 424c |           | 3                                     | 0.8                                   | 3                                    |
| 284  | 425  |           | 2                                     | 0.6                                   | 5                                    |
| 285  | 426  |           | 2                                     | 1                                     | 10                                   |
| 286  | 427  |           | 0.6                                   | 2                                     | 1                                    |
| 287  | 428  |           | 0.7                                   | 0.7                                   | 1                                    |

| Ex  | Cpd | Structure | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 288 | 429 |           | 4                                     | 0.9                                   | 1                                    |
| 289 | 430 |           | 5                                     | 0.7                                   | 1                                    |
| 290 | 431 |           | 5                                     | 5                                     |                                      |
| 291 | 432 |           | 2                                     | 1                                     | 3                                    |
| 292 | 432 |           | 2                                     | 0.6                                   | 1                                    |
| 293 | 434 |           | 4                                     | 0.6                                   | 2                                    |
| 294 | 435 |           | 3                                     | 0.6                                   | 1                                    |
| 295 | 436 |           | 5                                     | 0.8                                   | 5                                    |

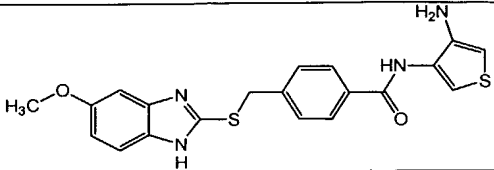
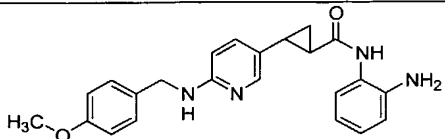
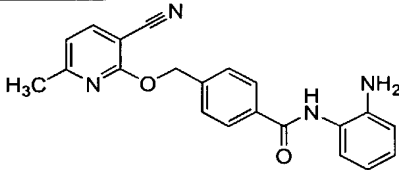
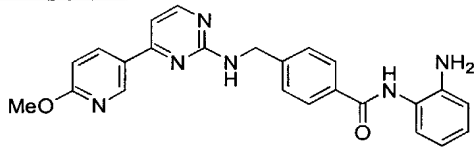
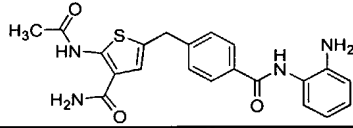
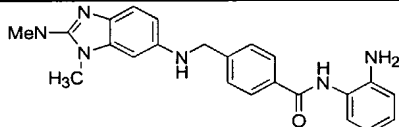
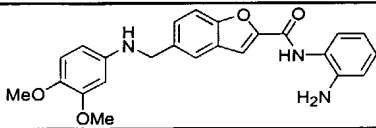
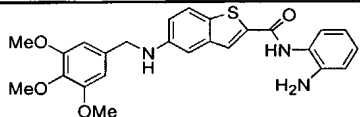
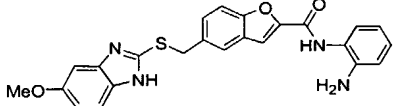
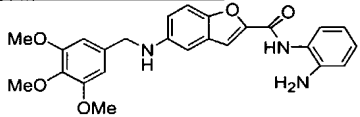
| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 296 | 437 |    | 3                                     | 0.4                                   | 1                                    |
| 297 | 438 |    | 5                                     | 0.6                                   | 1                                    |
| 298 | 439 |    | 3                                     | 0.4                                   | 1                                    |
| 299 | 440 |   | 4                                     | 0.1                                   | 2                                    |
| 300 | 441 |  | 2                                     | 0.8                                   | 2                                    |
| 301 | 442 |  | 17                                    | 0.4                                   | 1                                    |
| 302 | 443 |  |                                       |                                       |                                      |
| 303 | 444 |  |                                       |                                       |                                      |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 304 | 445 |    | 16                                    | 6                                     |                                      |
| 305 | 446 |    | 21                                    | 7                                     |                                      |
| 307 | 448 |    | 3                                     | 0.2                                   | 2                                    |
| 308 | 449 |    | 1                                     | 6                                     |                                      |
| 309 | 450 |   | 3                                     | 2                                     |                                      |
| 310 | 451 |  | 4                                     | 0.2                                   | 3                                    |
| 311 | 452 |  | 3                                     | 0.3                                   | 2                                    |
| 312 | 453 |  | 9999                                  | 37                                    |                                      |
| 313 | 454 |  | 4                                     | 2                                     | 5                                    |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 314 | 455 |    | 4                                     | 0.7                                   | 1                                    |
| 315 | 456 |    | 3                                     | 0.4                                   | 8888                                 |
| 316 | 457 |    | 9999                                  | 9999                                  |                                      |
| 317 | 458 |    | 3                                     | 0.3                                   | 2                                    |
| 318 | 459 |   | 4                                     | 0.3                                   | 1                                    |
| 319 | 460 |  | 3                                     | 1                                     | 1                                    |
| 320 | 461 |  | 1.4                                   | 0.3                                   | 1                                    |
| 321 | 462 |  | 4                                     | 0.3                                   | 1                                    |
| 322 | 463 |  | 12                                    | 6                                     |                                      |

| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 323 | 464 |    | 4                                     | 11                                    |                                      |
| 324 | 465 |    | 2                                     | 9999                                  | 9999                                 |
| 325 | 466 |    | 3                                     | 2                                     | 1                                    |
| 326 | 467 |    | 4                                     | 0.4                                   | 2                                    |
| 327 | 468 |   | 2                                     | 8                                     | <1                                   |
| 426 | 571 |  | 4                                     | 11                                    |                                      |
| 427 | 572 |  | 1.5                                   | 5                                     | 5                                    |
| 428 | 573 |  | 7                                     | 0.4                                   | 1                                    |
| 429 | 574 |  | 13                                    | 0.7                                   | 3                                    |



| Ex  | Cpd | Structure   | Human HDAC-1<br>IC <sub>50</sub> (μM) | MTT (HCT116)<br>IC <sub>50</sub> (μM) | H4 Ac (T24)<br>EC <sub>50</sub> (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|--------------------------------------|
| 430 | 575 |    | 2                                     | 0.2                                   | 1                                    |
| 431 | 576 |    | 5                                     | 6                                     |                                      |
| 432 | 577 |    | 2                                     | 0.5                                   | 2                                    |
| 433 | 578 |    | 0.6                                   | 0.1                                   | 1                                    |
| 434 | 579 |   | 2                                     | 0.5                                   | 1                                    |
| 435 | 580 |  | 4                                     | 0.3                                   | <1                                   |
| 436 | 587 |  | 5                                     | 0.8                                   | 2                                    |
| 437 | 590 |  | 2                                     | 2                                     | 3                                    |
| 438 | 591 |  | 4                                     | 0.3                                   | <1                                   |
| 439 | 592 |  | 5                                     | 0.4                                   | <1                                   |

**Assay Example 2****Antineoplastic Effects of Histone Deacetylase Inhibitor on Human Tumor Xenografts *In Vivo***

**[0397]** Eight to ten week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in the flank area with  $2 \times 10^6$  preconditioned HCT116 human colorectal carcinoma cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under Forene anesthesia (Abbott Labs, Geneva, Switzerland). When the tumors reached a mean volume of 100 mm<sup>3</sup>, the mice were treated intravenously, subcutaneously, or intraperitoneally by daily injection, with a solution of the histone deacetylase inhibitor in an appropriate vehicle, such as PBS, DMSO/water, or Tween 80/water, at a starting dose of 10 mg/kg. The optimal dose of the HDAC inhibitor was established by dose response experiments according to standard protocols. Tumor volume was calculated every second day post infusion according to standard methods (e.g., Meyer et al., *Int. J. Cancer* **43**: 851-856 (1989)). Treatment with the HDAC inhibitors according to the invention caused a significant reduction in tumor weight and volume relative to controls treated with vehicle only (i.e., no HDAC inhibitor). In addition, the level of histone acetylation when measured was significantly elevated relative to controls. Data for selected compounds are presented in Table 6. FIG. 1 shows the full experimental results for compound **106**, which inhibits tumor growth by 80%. Figs. 2-10 show the results of additional compounds tested.

**Table 6****Antitumor Activity in HCT 116 Colorectal Tumor Model *In Vivo***

| <b>Compound</b> | <b>% Inhibition of Tumor Growth</b> |
|-----------------|-------------------------------------|
| 106             | 80 <sup>a</sup>                     |
| 126             | 62 <sup>b</sup>                     |
| 9               | 51 <sup>b</sup>                     |
| 87              | 30 <sup>b</sup>                     |
| 157             | 66 <sup>a</sup>                     |
| 167             | 58 <sup>a</sup>                     |
| 15              | 26 <sup>b</sup>                     |
| 168             | 26 <sup>b</sup>                     |
| 16              | 50 <sup>b</sup>                     |
| 154             | 23 <sup>a</sup>                     |
| 98              | 52 <sup>a</sup>                     |

a: 20 mg/kg i.p.

b: 40 mg/kg i.p.

**Table 7**

**Antineoplastic Effects Of Histone Deacetylase  
Inhibitors On Nude Mice Xenograft Models**

| cpd  | % Inhibition Of Tumor Growth |                |                |                |                |
|------|------------------------------|----------------|----------------|----------------|----------------|
|      | A 549 (p.o.)                 | SW48 (p.o.)    | A 549 (i.p.)   | HCT 116 (i.p.) | SW 48 (i.p.)   |
| 106  | 40% (70 mg/kg)               | 16% (60 mg/kg) | -              | -              | -              |
| 164  | 42% (70 mg/kg)               | 62% (60 mg/kg) | -              | 37% (20 mg/kg) | 99% (25 mg/kg) |
| 228  | 45% (70 mg/kg)               | 25% (60 mg/kg) | 64% (20 mg/kg) | 45% (20 mg/kg) | 68% (20 mg/kg) |
| 424b | 67% (50 mg/kg)               | 78% (30 mg/kg) | 60% (50 mg/kg) | 77% (75 mg/kg) | 68% (25 mg/kg) |

**Assay Example 3**

**Combined Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells *In Vivo***

**[0398]** The purpose of this example is to illustrate the ability of the combined use of a histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to enhance inhibition of tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

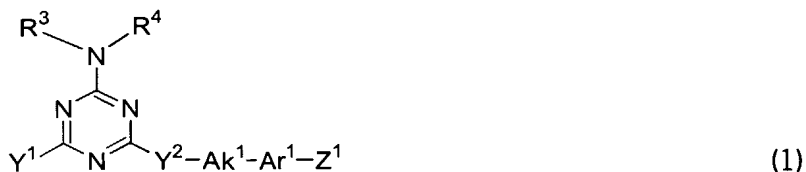
**[0399]** As described in Example 126, mice bearing implanted HCT116 tumors (mean volume 100 mm<sup>3</sup>) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

**[0400]** Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice are similarly established which receive no treatment (e.g., saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

**[0401]** Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitor according to the invention causes a significant reduction in tumor weight and volume relative to controls.

**We claim:**

1. A histone deacetylase inhibitor of formula (1):



or a pharmaceutically acceptable salt thereof, wherein

$\text{R}^3$  and  $\text{R}^4$  are independently selected from the group consisting of hydrogen,  $\text{L}^1$ ,  $\text{Cy}^1$ , and  $-\text{L}^1\text{-Cy}^1$ , wherein

$\text{L}^1$  is  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_2\text{-C}_6$  heteroalkyl, or  $\text{C}_3\text{-C}_6$  alkenyl; and

$\text{Cy}^1$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; or

$\text{R}^3$  and  $\text{R}^4$  are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring is optionally substituted, and optionally forms part of a bicyclic ring system, or is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems is optionally substituted;

$\text{Y}^1$  is selected from the group consisting of  $-\text{N}(\text{R}^1)(\text{R}^2)$ ,  $-\text{CH}_2\text{-C}(\text{O})\text{-N}(\text{R}^1)(\text{R}^2)$ , halogen, and hydrogen, wherein

$\text{R}^1$  and  $\text{R}^2$  are independently selected from the group consisting of hydrogen,  $\text{L}^1$ ,  $\text{Cy}^1$ , and  $-\text{L}^1\text{-Cy}^1$ , wherein

$\text{L}^1$  is  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_2\text{-C}_6$  heteroalkyl, or  $\text{C}_3\text{-C}_6$  alkenyl; and

$\text{Cy}^1$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; or

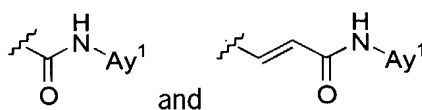
$\text{R}^1$  and  $\text{R}^2$  are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the

group consisting of C, O, S, and N, and wherein the ring is optionally substituted, and optionally forms part of a bicyclic ring system, or is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems is optionally substituted;  $Y^2$  is a chemical bond or  $N(R^0)$ , where  $R^0$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

$Ak^1$  is  $C_1-C_6$  alkylene,  $C_1-C_6$ -heteroalkylene (preferably, in which one  $-CH_2-$  is replaced with  $-NH-$ , and more preferably  $-NH-CH_2-$ ),  $C_2-C_6$  alkenylene or  $C_2-C_6$  alkynylene;

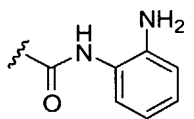
$Ar^1$  is arylene or heteroarylene, either of which is optionally substituted; and

$Z^1$  is selected from the group consisting of



wherein  $Ay^1$  is aryl or heteroaryl, each of which is optionally substituted.

2. The compound according to claim 1 wherein  $Ay^1$  is phenyl or thienyl, each substituted with  $-OH$  or  $-NH_2$ .
3. The compound according to claim 2 wherein the amino or hydroxy substituent is ortho to the nitrogen to which  $Ay^2$  is attached.
4. The compound according to claim 1 wherein  $Ay^1$  is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl.
5. The compound according to claim 1 wherein  $Z^1$  is



6. The compound according to claim 1 wherein  $Ar^1$  is phenylene.
7. The compound according to claim 1 wherein  $Ak^1$  is alkylene.
8. The compound according to claim 1 wherein  $Ak^1$  is methylene.

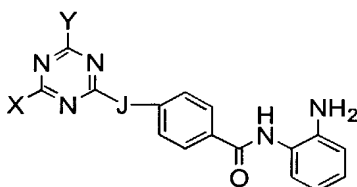
9. The compound according to claim 1 wherein  $Y^2$  is -NH.
10. The compound according to claim 1 wherein  $Y^1$  is  $-N(R^1)(R^2)$  or  $-CH_2-C(O)-N(R^1)(R^2)$ .
11. The compound according to claim 10 wherein  $R^1$  and/or  $R^2$  are hydrogen.
12. The compound according to claim 10 wherein  $R^1$  and/or  $R^2$  are  $C_1-C_6$  alkyl or  $C_2-C_6$  alkenyl.
13. The compound according to claim 10 wherein  $R^1$  and/or  $R^2$  are allyl.
14. The compound according to claim 10 wherein  $R^1$  and/or  $R^2$  are aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally are substituted and optionally fused to one or two aryl rings.
15. The compound according to claim 14 wherein  $R^1$  and/or  $R^2$  are independently are phenyl, pyridyl, or pyrrolyl.
16. The compound according to claim 10 wherein  $R^1$  and/or  $R^2$  are independently cycloalkyl which is optionally substituted and optionally fused to one or two aryl rings
17. The compound according to claim 16 wherein  $R^1$  and/or  $R^2$  are independently cyclopropyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted and optionally fused to one or two aryl rings.
18. The compound according to claim 16 wherein  $R^1$  and/or  $R^2$  are independently cyclopropyl, cyclopentyl, or cyclohexyl.
19. The compound according to claim 1 wherein  $R^3$  and/or  $R^4$  are hydrogen.
20. The compound according to claim 1 wherein  $R^3$  and/or  $R^4$  are independently  $C_1-C_6$  alkyl or  $C_2-C_6$  alkenyl.
21. The compound according to claim 20 wherein  $R^3$  and/or  $R^4$  are allyl.

22. The compound according to claim 1 wherein R<sup>3</sup> and/or R<sup>4</sup> are independently aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which is optionally substituted and optionally fused to one or two aryl rings.
23. The compound according to claim 22 wherein R<sup>3</sup> and/or R<sup>4</sup> are independently phenyl, pyridyl, or pyrrolyl.
24. The compound according to claim 1 wherein R<sup>3</sup> and/or R<sup>4</sup> are independently cycloalkyl.
25. The compound according to claim 24 wherein R<sup>3</sup> and/or R<sup>4</sup> are independently cyclopropyl, cyclopentyl, or cyclohexyl, which is optionally substituted and optionally fused to one or two aryl rings.
26. The compound according to claim 24 wherein R<sup>3</sup> and/or R<sup>4</sup> are independently cyclopropyl, cyclopentyl, or cyclohexyl.
27. The compound according to claim 1 wherein L<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> heteroalkyl, or C<sub>3</sub>-C<sub>6</sub> alkenyl.
28. The compound according to claim 27 wherein L<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkylene
29. The compound according to claim 27 wherein L<sup>1</sup> is methylene or ethylene.
30. The compound according to claim 27 wherein L<sup>1</sup> is allyl.
31. The compound according to claim 1 wherein Cy<sup>1</sup> is heterocyclyl that is optionally substituted and optionally fused to one or two aryl rings
32. The compound according to claim 31 wherein Cy<sup>1</sup> is piperidine, pyrrolidine, piperazine, or morpholine, each of which is optionally substituted and optionally fused to one or two aryl rings.
33. The compound according to claim 31 wherein Cy<sup>1</sup> is piperidine, pyrrolidine, piperazine, or morpholine
34. The compound according to claim 1 wherein Cy<sup>1</sup> is cycloalkyl.

35. The compound according to claim 34 wherein Cy<sup>1</sup> is cyclopropyl, cyclopentyl, or cyclohexyl.
36. The compound according to claim 1 wherein Cy<sup>1</sup> is aryl or heteroaryl each of which is optionally substituted and is optionally fused to one or two aryl rings.
37. The compound according to claim 36 wherein Cy<sup>1</sup> is phenyl, pyridyl, or pyrrolyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
38. The compound according to claim 36 wherein Cy<sup>1</sup> is phenyl, pyridyl, or pyrrolyl.
39. The compound according to claim 36 wherein Cy<sup>1</sup> is fused to one or two benzene rings.
40. The compound according to claim 1 wherein Cy<sup>1</sup> has between one and about five substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and halo.
41. The compound according to claim 40 wherein the substituents independently selected from are methyl, methoxy, and fluoro.
42. The compound according to claim 1 wherein R<sup>1</sup> and R<sup>2</sup> together and/or R<sup>3</sup> and R<sup>4</sup> together, each with the adjacent nitrogen atom, form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring is optionally substituted and is optionally fused to one or two aryl rings.
43. The compound according to claim 42 wherein the 5- or 6-membered ring is pyrrolidine, piperidine, piperazine, or morpholine, and wherein each ring is optionally substituted and optionally fused to an aryl ring.
44. The compound according to claim 43 wherein the aryl ring is benzene.
45. The compound according to claim 43 wherein the substituent comprises an aryl or C<sub>3</sub>-C<sub>12</sub> cycloalkyl ring, either of which is optionally substituted and optionally fused to a C<sub>3</sub>-C<sub>12</sub> cycloalkyl, aryl, heteroaryl, or heterocyclic ring.



46. The compound according to claim 44, wherein the substituent is phenyl, phenylmethyl, or phenylethyl, the phenyl ring of each of which is optionally fused to a C<sub>1</sub>-C<sub>12</sub> cycloalkyl, aryl, or heterocyclic ring.
47. A histone deacetylase inhibitor of formula 1(a):



(1a)

or a pharmaceutically acceptable salt thereof, wherein

J is C<sub>1</sub>-C<sub>3</sub>-hydrocarbonyl, -N(R<sup>20</sup>)-, -N(R<sup>20</sup>)-CH<sub>2</sub>-, -O-, or -O-CH<sub>2</sub>-;

R<sup>20</sup> is -H or -Me;

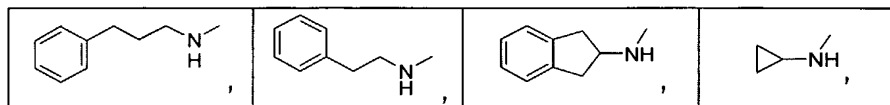
X and Y are independently selected from -NH<sub>2</sub>, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A-(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>n</sub>-B-;

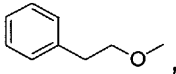

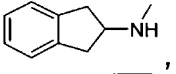

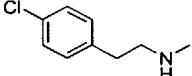
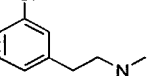
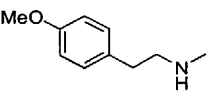
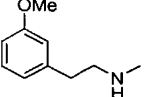
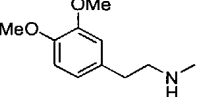
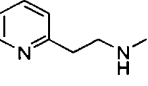
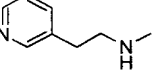
A is H, C<sub>1</sub>-C<sub>6</sub>-alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -O-, or a direct bond; and


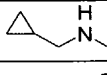
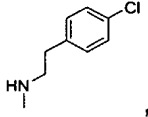
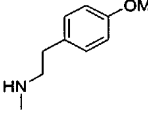
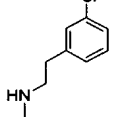
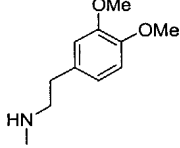
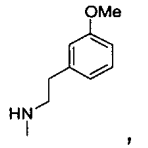
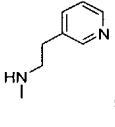

n is 0 (in which case A is directly bonded to B) or 1.

48. The compound according to claim 47 wherein A is phenyl optionally substituted with one or more moieties selected from halo and methoxy, and B is -NH-.
49. The compound according to claim 47 wherein A is selected from cyclopropyl, pyridinyl, and indanyl.
50. The compound according to claim 47 wherein J is -NH-CH<sub>2</sub>-, -O-CH<sub>2</sub>-, -N(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH=CH-, or -CH<sub>2</sub>-CH<sub>2</sub>-.
51. The compound according to claim 47 wherein R<sup>20</sup> is -H.
52. The compound according to claim 47 wherein X is selected from

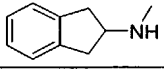
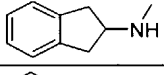

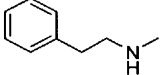
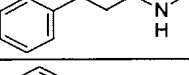
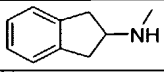
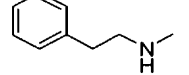

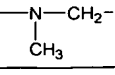
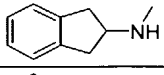
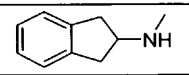
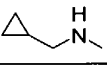
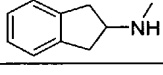
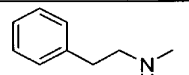


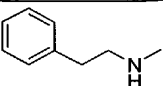

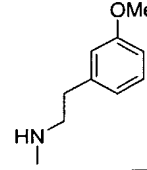

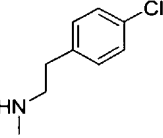

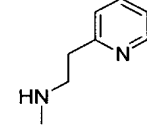

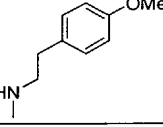

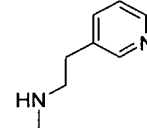

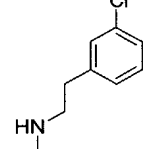
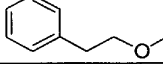


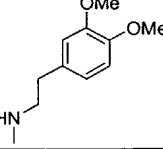
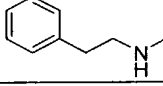

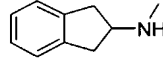

|   |   |  |   |
|---|---|--|---|
|  |  | -OMe,  |  |
|  | -NH <sub>2</sub>  |  |  |
|  |  |  |  |
| and   |  |  |   |

and Y is selected from

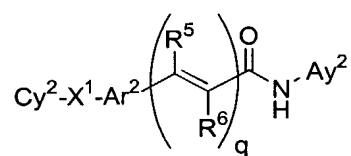
|  |  |   |  |
|--|--|---|--|
| -NH <sub>2</sub> ,   |   |   | n-BuNH,  |
| MeOCH <sub>2</sub> CH <sub>2</sub> NH,   |   |   |   |
|  |  |  |  |
| -H   | Me   | -OMe  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> NH-                                  |
| and  | CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -NH-                              |   |  |

53. The compound according to claim 47 wherein J, X, and Y are selected from the following combinations:

| Cpd | J   | X   | Y                | Cpd | J                                  | X   | Y   |
|-----|---|---|------------------|-----|------------------------------------|---|---|
| 204 | -NH-  |  | -NH <sub>2</sub> | 220 | -CH=CH-                            | -NH <sub>2</sub>  | -NH <sub>2</sub> -  |
| 207 | -OCH <sub>2</sub> -   |  | -NH <sub>2</sub> | 223 | -CH=CH-                            |  | -NH <sub>2</sub>  |
| 210 | -NHCH <sub>2</sub> -  |  | -H               | 224 | -CH <sub>2</sub> CH <sub>2</sub> - | -NH <sub>2</sub>  | -NH <sub>2</sub>  |
| 212 | -NHCH <sub>2</sub> -  | -OMe  | -OMe             | 470 | -NHCH <sub>2</sub> -               |  | NH <sub>2</sub>   |
| 214 | -NHCH <sub>2</sub> -  |  | -OMe             | 471 | -NHCH <sub>2</sub> -               |  |  |
| 216 |  |  | -Me              | 472 | -NHCH <sub>2</sub> -               |  |  |
| 218 | -NHCH <sub>2</sub> -  |  | -Me              | 473 | -NHCH <sub>2</sub> -               |  | n-BuNH  |

| Cpd | J                    | X   | Y  | Cpd | J                    | X   | Y   |
|-----|----------------------|---|--|-----|----------------------|---|---|
| 474 | -NHCH <sub>2</sub> - |  | MeO(CH <sub>2</sub> ) <sub>2</sub> NH  | 479 | -NHCH <sub>2</sub> - |    |    |
| 475 | -NHCH <sub>2</sub> - |  |   | 480 | -NHCH <sub>2</sub> - |    |    |
| 476 | -NHCH <sub>2</sub> - |  |   | 481 | -NHCH <sub>2</sub> - |    |    |
| 477 | -NHCH <sub>2</sub> - |  |   | 482 | -NHCH <sub>2</sub> - |    |    |
| 478 | -NHCH <sub>2</sub> - |  |  | 483 | -NHCH <sub>2</sub> - |    | Me  |
|     |                      |   |  | 484 | -NHCH <sub>2</sub> - |    | NH <sub>2</sub>   |
|     |                      |   |  | and |                      |   |   |
|     |                      |   |  | 485 | -NHCH <sub>2</sub> - |  |  |

54. A histone deacetylase inhibitor of formula (2):



(2)

or a pharmaceutically acceptable salt thereof, wherein

Cy<sup>2</sup> is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X<sup>1</sup> is selected from the group consisting of a covalent bond, M<sup>1</sup>-L<sup>2</sup>-M<sup>1</sup>, and L<sup>2</sup>-M<sup>2</sup>-L<sup>2</sup> wherein

$L^2$ , at each occurrence, is independently selected from the group consisting of a chemical bond,  $C_1-C_4$  alkylene,  $C_2-C_4$  alkenylene, and  $C_2-C_4$  alkynylene, provided that  $L^2$  is not a chemical bond when  $X^1$  is  $M^1-L^2-M^1$ ;

$M^1$ , at each occurrence, is independently selected from the group consisting of  $-O-$ ,  $-N(R^7)-$ ,  $-S-$ ,  $-S(O)-$ ,  $S(O)_2-$ ,  $-S(O)_2N(R^7)-$ ,  $-N(R^7)-S(O)_2-$ ,  $-C(O)-$ ,  $-C(O)-NH-$ ,  $-NH-C(O)-$ ,  $-NH-C(O)-O-$  and  $-O-C(O)-NH-$ , wherein  $R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

$M^2$  is selected from the group consisting of  $M^1$ , heteroarylene, and heterocyclylene, either of which rings is optionally substituted;

$Ar^2$  is arylene or heteroarylene, each of which is optionally substituted;

$R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

$q$  is 0 or 1; and

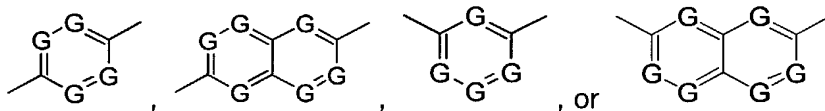
$Ay^2$  is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which  $Ay^2$  is attached) and further optionally substituted;

provided that when  $Cy^2$  is naphthyl,  $X^1$  is  $-CH_2-$ ,  $Ar^2$  is phenyl,  $R^5$  and  $R^6$  are H, and  $q$  is 0 or 1,  $Ay^2$  is not phenyl or *o*-hydroxyphenyl.

55. The compound according to claim 54 wherein when  $Ay^2$  is *o*-phenol optionally substituted by halo, nitro, or methyl,  $Ar^2$  is optionally substituted phenyl,  $X^1$  is  $-O-$ ,  $-CH_2-$ ,  $-S-$ ,  $-S-CH_2-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-C(O)-$ , or  $-OCH_2-$ , then  $Cy^2$  is not optionally substituted phenyl or naphthyl.
56. The compound according to claim 54 wherein when  $Ay^2$  is *o*-anilinyll optionally substituted by halo,  $C_1-C_6$ -alkyl,  $C_1-C_6$ -alkoxy or  $-NO_2$ ,  $q$  is 0,  $Ar^2$  is phenyl, and  $X^1$  is  $-CH_2-$ , then  $Cy^2$  is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).
57. The compound according to claim 54 wherein when  $X^1$  is  $-CH_2-$ ,  $Ar^2$  is optionally substituted phenyl,  $q$  is 1, and  $R^6$  is H, then  $Cy^2$  is not optionally substituted imidazole.

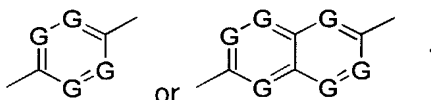
58. The compound according to claim 54 wherein when  $\text{Ar}^2$  is amino or hydroxy substituted phenyl,  $\text{X}^1$  is  $\text{C}_0\text{-C}_8\text{-alkyl-X}^{1a}$ - $\text{C}_0\text{-C}_8\text{-alkyl}$ , wherein  $\text{X}^{1a}$  is  $-\text{CH}_2-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NH}-$ ,  $-\text{C}(\text{O})-$ , then  $\text{Cy}^2$  is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.
59. The compound according to claim 54 wherein when  $\text{Ay}^2$  is o-phenol,  $\text{Ar}^2$  is substituted phenyl,  $\text{X}^1$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{CH}_2-$ ,  $-\text{O-CH}_2-$ ,  $-\text{S-CH}_2-$ , or  $-\text{C}(\text{O})-$ , and  $\text{R}^5$  and  $\text{R}^6$  are H, then  $\text{Cy}^2$  is not optionally substituted naphthyl.
60. The compound according to claim 54 wherein when  $\text{Ay}^2$  is o-anilinyll, q is 0,  $\text{Ar}^2$  is unsubstituted phenyl,  $\text{X}^1$  is  $-\text{CH}_2-$ , then  $\text{Cy}^2$  is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.
61. The compound according to claim 54 wherein  $\text{Ay}^2$  is phenyl or thienyl, each substituted with  $-\text{OH}$  or  $-\text{NH}_2$ .
62. The compound according to claim 54 wherein the amino or hydroxy substituent is ortho to the nitrogen to which  $\text{Ay}^2$  is attached.
63. The compound according to claim 54 wherein  $\text{Ay}^2$  is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl.
64. The compound according to claim 54 wherein  
q is 1;  
 $\text{M}^1$ , at each occurrence, is selected from the group consisting of  $-\text{N}(\text{R}^7)-$ ,  $-\text{S}-$ ,  $-\text{C}(\text{O})\text{-NH}-$ , and  $-\text{O-C}(\text{O})\text{-NH}-$ , where  $\text{R}^7$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and  
 $\text{Ay}^2$  is anilinyll, which is optionally substituted.
65. The compound according to claim 64 wherein the  $-\text{NH}_2$  group of  $\text{Ay}^2$  is in an ortho position with respect to the nitrogen atom to which  $\text{Ay}^2$  is attached.
66. The compound according to claim 65 wherein  $\text{R}^5$  and  $\text{R}^6$  are independently selected from the group consisting of hydrogen and  $\text{C}_1\text{-C}_4$  alkyl.
67. The compound according to claim 65 wherein  $\text{R}^5$  and  $\text{R}^6$  are hydrogen.

68. The compound according to claim 54 wherein  $\text{Ar}^2$  has the formula



and wherein G, at each occurrence, is independently N or C, and C is optionally substituted.

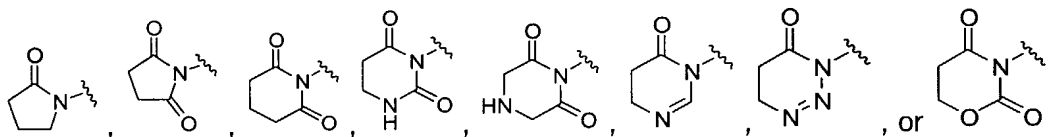
69. The compound according to claim 68 wherein  $\text{Ar}^2$  has the formula



70. The compound according to claim 54 wherein  $\text{Ar}^2$  is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolyne.
71. The compound according to claim 54 wherein  $\text{X}^1$  is a chemical bond.
72. The compound according to claim 54 wherein  $\text{X}^1$  is  $\text{L}^2\text{-M}^2\text{-L}^2$ , and  $\text{M}^2$  is selected from the group consisting of -NH-, -N(CH<sub>3</sub>)-, -S-, -C(O)-N(H)-, and -O-C(O)-N(H)-.
73. The compound according to claim 54 wherein  $\text{X}^1$  is  $\text{L}^2\text{-M}^2\text{-L}^2$ , where at least one occurrence of  $\text{L}^2$  is a chemical bond.
74. The compound according to claim 54 wherein  $\text{X}^1$  is  $\text{L}^2\text{-M}^2\text{-L}^2$ , where at least one occurrence of  $\text{L}^2$  is alkylene, preferably methylene.
75. The compound according to claim 54 wherein  $\text{X}^1$  is  $\text{L}^2\text{-M}^2\text{-L}^2$ , where at least one occurrence of  $\text{L}^2$  is alkenylene.
76. The compound according to claim 54 wherein  $\text{X}^1$  is  $\text{M}^1\text{-L}^2\text{-M}^1$  and  $\text{M}^1$  is selected from the group consisting of -NH-, -N(CH<sub>3</sub>)-, -S-, and -C(O)-N(H)-.
77. The compound according to claim 54 wherein  $\text{Cy}^2$  is aryl or heteroaryl, each optionally substituted.
78. The compound according to claim 54 wherein  $\text{Cy}^2$  is phenyl, pyridyl, imidazolyl, or quinolyl, each of which is optionally substituted.

79. The compound according to claim 54 wherein Cy<sup>2</sup> is heterocyclyl.

80. The compound according to claim 54 wherein Cy<sup>2</sup> is

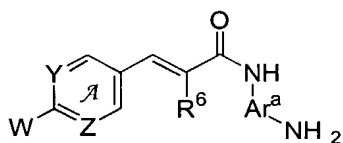


each of which is optionally substituted and is optionally fused to one or two aryl rings.

81. The compound according to claim 54 wherein Cy<sup>2</sup> has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy.

82. The compound according to claim 54 wherein the substituents are selected from methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl

83. The compound of claim 54 of structural formula (2a):



(2a)

wherein

Ar<sup>a</sup> is phenyl or thienyl;

R<sup>6</sup> is H, or C<sub>1</sub>-C<sub>6</sub>-alkyl (preferably -CH<sub>3</sub>);

Y and Z are independently -CH= or -N=;

W is halo, (V<sup>1</sup>-L<sup>4</sup>)<sub>t</sub>-V-L<sup>3</sup>;

L<sup>3</sup> is a direct bond, -C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl, -(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)<sub>m1</sub>-X'-(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)<sub>m2</sub>, -NH-(C<sub>0</sub>-C<sub>3</sub>-hydrocarbyl), (C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)-NH-, or -NH-(C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl)-NH-;

m<sub>1</sub> and m<sub>2</sub> are independently 0 or 1;

X' is -N(R<sup>21</sup>)-, -C(O)N(R<sup>21</sup>)-, N(R<sup>21</sup>)C(O)-, -O-, or -S-;

R<sup>21</sup> is -H, V''-(C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>c</sub>;

L<sup>4</sup> is (C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>a</sub>-M-(C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl)<sub>b</sub>;

a and b are independently 0 or 1;

M is -NH-, -NHC(O)-, -C(O)NH-, -C(O)-, -SO<sub>2</sub>-, -NHSO<sub>2</sub>-, or -SO<sub>2</sub>NH-

V, V', and V'' are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the  $\mathcal{A}$  and Ar<sup>a</sup> rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

84. The compound according to claim 83 wherein:

Y and Z are -CH= and R<sup>6</sup> is H;

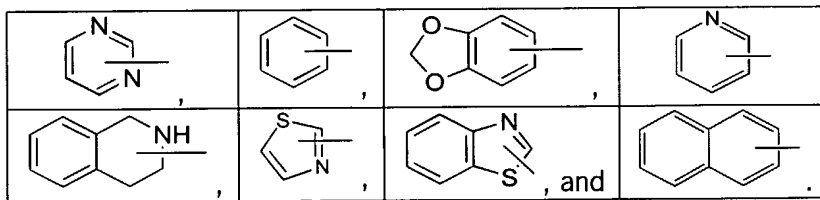
W is VL<sup>3</sup>;

L<sup>3</sup> is -NH-CH- or -CH-NH-;

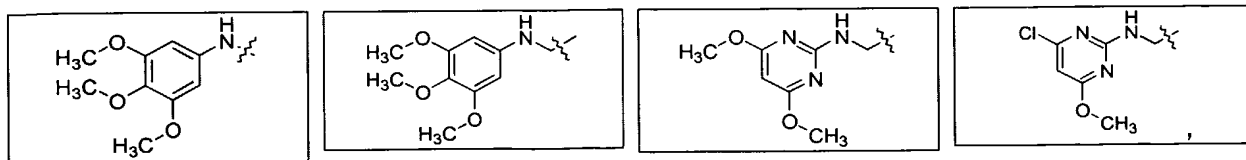
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl, C<sub>1</sub>-C<sub>6</sub>-hydrocarbyl-oxy or -thio (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

Ar<sup>a</sup> is phenyl and the amino moieties to which it is bound are ortho to each other.

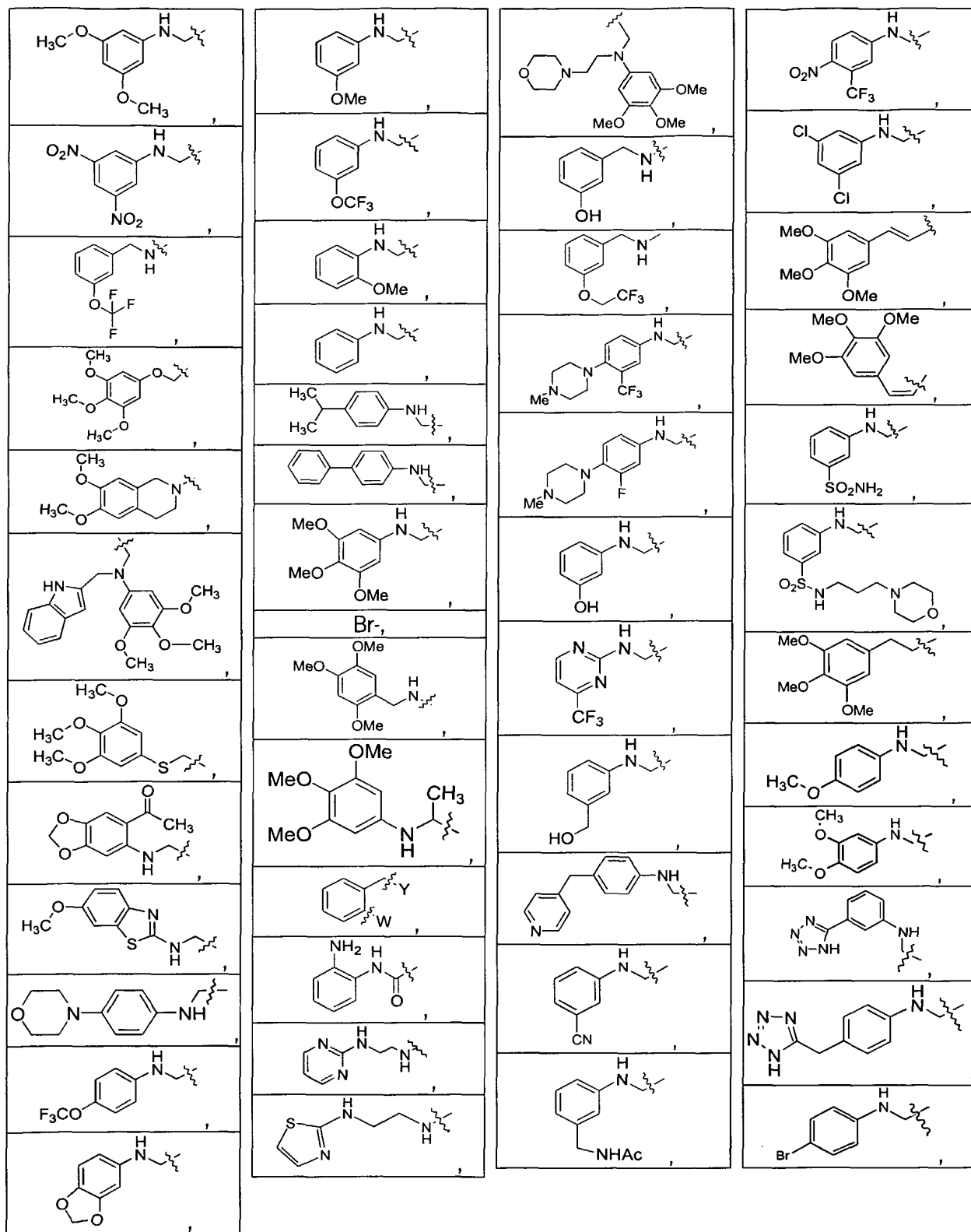
85. The compound according to claim 83 wherein V is an optionally substituted ring moiety selected from:

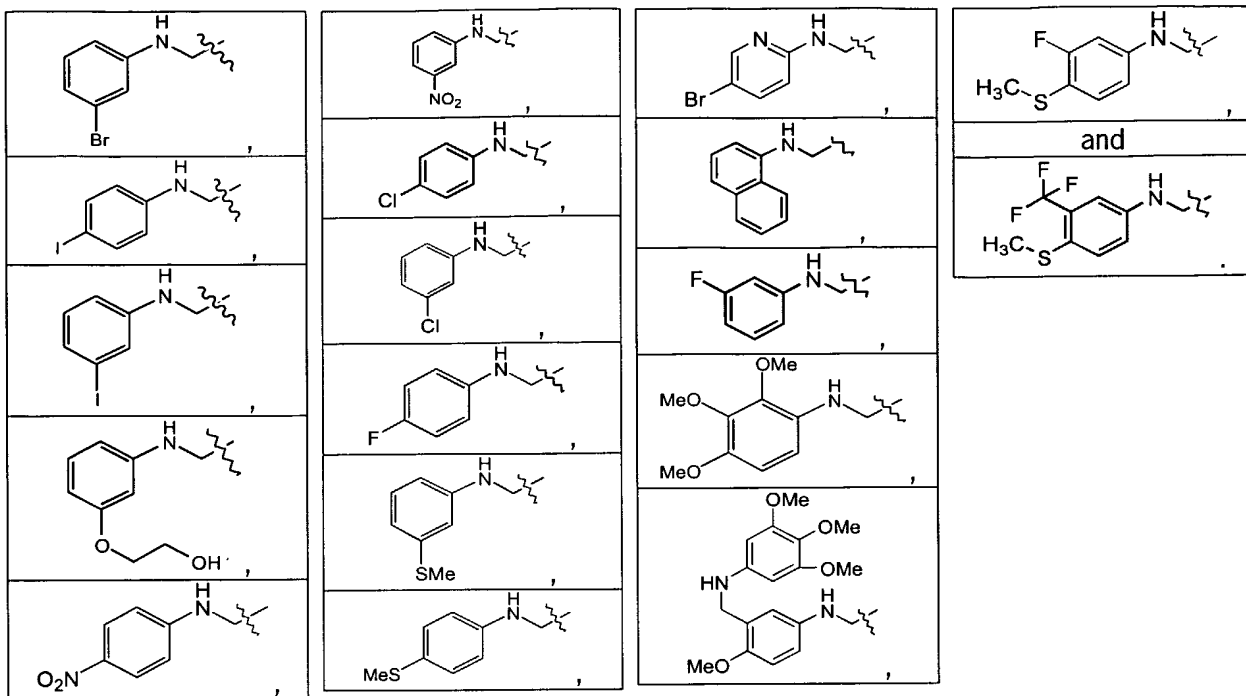


86. The compound according to claim 83 wherein W is selected from:









87. The compound according to claim 83 wherein the  $\mathcal{A}$  and  $\text{Ar}^a$  rings are not further substituted.

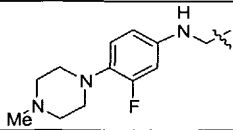
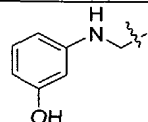
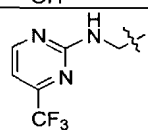
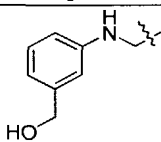
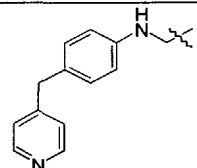
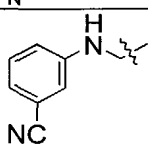
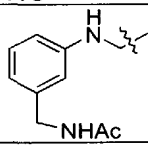
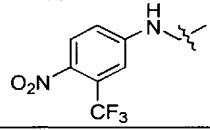
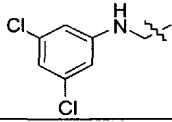
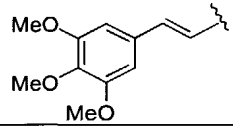
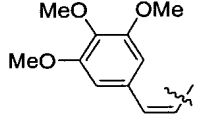
88. The compound according to claim 83 selected from the following, in which, unless expressly displayed otherwise,  $\text{Ar}^a$  is phenyl:

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 481 |   | CH | CH | H              |
| 484 |   |    |    |                |
| 492 |   | CH | CH | H              |
| 493 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 494 |   | CH | CH | H              |
| 495 |   | CH | CH | H              |
| 496 |   | CH | CH | H              |
| 497 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 498 |   | CH | CH | H              |
| 499 |   | CH | CH | H              |
| 500 |   | CH | CH | H              |
| 501 |   | CH | CH | H              |
| 502 |   | CH | CH | H              |
| 503 |   | CH | CH | H              |
| 504 |   | CH | CH | H              |
| 505 |   | CH | CH | H              |
| 506 |   | CH | CH | H              |
| 507 |   | CH | CH | H              |
| 508 |   | CH | CH | H              |
| 509 |   | CH | CH | H              |
| 510 |   | CH | CH | H              |

| Cpd | W   | Y  | Z  | R <sup>6</sup>  |
|-----|-----|----|----|-----------------|
| 511 |     | CH | CH | H               |
| 512 |     | CH | N  | H               |
| 516 | Br- | CH | CH | CH <sub>3</sub> |
| 517 |     | CH | CH | CH <sub>3</sub> |
| 518 |     | CH | CH | CH <sub>3</sub> |
| 519 |     | CH | CH | H               |
| 520 |     | CH | CH | H               |
| 521 |     | N  | CH | H               |
| 522 |     | N  | CH | H               |
| 523 |     | CH | CH | H               |
| 524 |     | N  | CH | H               |
| 525 |     | N  | CH | H               |
| 526 |     | CH | CH | H               |

| Cpd | W   | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 527 |    | CH | CH | H              |
| 528 |    | CH | CH | H              |
| 529 |    | CH | CH | H              |
| 530 |    | CH | CH | H              |
| 531 |    | CH | CH | H              |
| 532 |   | CH | CH | H              |
| 533 |  | CH | CH | H              |
| 534 |  | CH | CH | H              |
| 535 |  | CH | CH | H              |
| 536 |  | CH | CH | H              |
| 537 |  | CH | CH | H              |

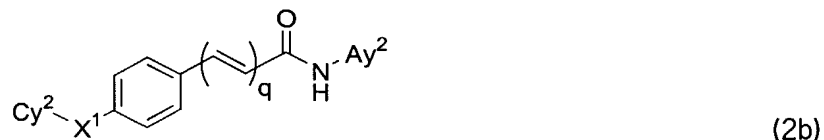
| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 538 |   | CH | CH | H              |
| 539 |   | CH | CH | H              |
| 540 |   | CH | CH | H              |
| 541 |   | CH | CH | H              |
| 542 |   | CH | CH | H              |
| 543 |   | CH | CH | H              |
| 544 |   | CH | CH | H              |
| 545 |   | CH | CH | H              |
| 546 |   | CH | CH | H              |
| 547 |   | CH | CH | H              |
| 548 |   | CH | CH | H              |
| 549 |   | CH | CH | H              |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 550 |   | CH | CH | H              |
| 551 |   | CH | CH | H              |
| 552 |   | CH | CH | H              |
| 553 |   | CH | CH | H              |
| 554 |   | CH | CH | H              |
| 555 |   | CH | CH | H              |
| 556 |   | CH | CH | H              |
| 557 |   | CH | CH | H              |
| 558 |   | CH | CH | H              |
| 559 |   | CH | CH | H              |
| 560 |   |    |    |                |
| 561 |   |    |    |                |

| Cpd | W | Y  | Z  | R <sup>6</sup> |
|-----|---|----|----|----------------|
| 562 |   | CH | CH | H              |
| 563 |   | CH | CH | H              |
| 564 |   |    |    |                |
| 565 |   | CH | CH | H              |
| 566 |   | CH | CH | H              |
| 567 |   |    |    |                |
| 568 |   |    |    |                |
| 569 |   | CH | N  | H              |
| 570 |   |    |    |                |

89. The compound according to claim 88 wherein the amide nitrogen and the amino nitrogen bound to Ar<sup>a</sup> are *ortho* to each other)

90. The compound according to claim 54, the invention comprises compounds of the formula (2b):



or a pharmaceutically acceptable salt thereof, wherein

Ay² is phenyl or thienyl, each substituted at the ortho position with -NH₂ or -OH and each further optionally substituted with one to three substituents independently selected from -NH₂, -OH, and halo;

q is 0 or 1;

X¹ is selected from -CH₂-, -NH-CH₂-, and -S-CH₂-;

Cy² is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH₃-, CH₃O-, phenyl optionally substituted with one to three CH₃O-, morphylinyl, morphylinyl-C₁-C₃-alkoxy, cyano, and CH₃C(O)NH-;

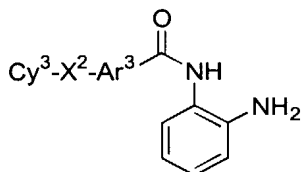
provided that when Cy² is naphthyl, X¹ is -CH₂-, and q is 0 or 1, Ay² is not o-hydroxyphenyl.

91. The compound according to claim 90 wherein Ay² is selected from:



92. The compound according to claim 90 wherein Cy² is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinoxolyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH₃O-.
93. The compound according to claim 90 wherein Cy² is phenyl substituted with one to three CH₃O-.

94. A histone deacetylase inhibitor of formula (3):



(3)

or a pharmaceutically acceptable salt thereof, wherein

$Ar^3$  is arylene or heteroarylene, either of which is optionally substituted;

$Cy^3$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

provided that when  $Cy^3$  is a cyclic moiety having  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ , or  $-S(O)_2-$  in the ring, then  $Cy^3$  is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

$X^2$  is selected from the group consisting of a chemical bond,  $L^3$ ,  $W^1-L^3$ ,  $L^3-W^1$ ,  $W^1-L^3-W^1$ , and  $L^3-W^1-L^3$ , wherein

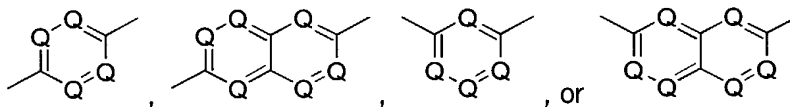
$W^1$ , at each occurrence, is S, O, or  $N(R^9)$ , where  $R^9$  is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

$L^3$  is  $C_1-C_4$  alkylene,  $C_2-C_4$  alkenylene, or  $C_2-C_4$  alkynylene;

provided that  $X^2$  does not comprise a  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ , or  $-S(O)_2-$  group;

and further provided that when  $Cy^3$  is pyridine, then  $X^2$  is  $L^3$ ,  $W^1-L^3$ , or  $L^3-W^1$ .

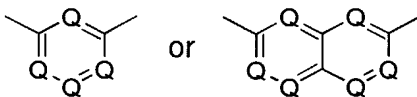
95. The compound according to claim 94 wherein  $Ar^3$  has the structure:



wherein Q, at each occurrence, is independently N or C, and C is optionally substituted;

96. The compound according to claim 94 wherein  $X^2$  is selected from the group consisting of  $L^3$ ,  $W^1-L^3$ ,  $L^3-W^1$ ,  $W^1-L^3-W^1$ , and  $L^3-W^1-L^3$ .

97. The compound according to claim 94 wherein when  $X^2$  is a chemical bond, then  $Ar^3$  is not

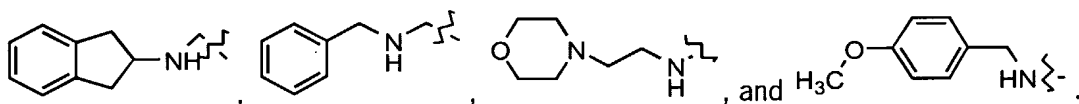


and  $Cy^3$  is not the radical of a substituted or unsubstituted diazepine or benzofuran.

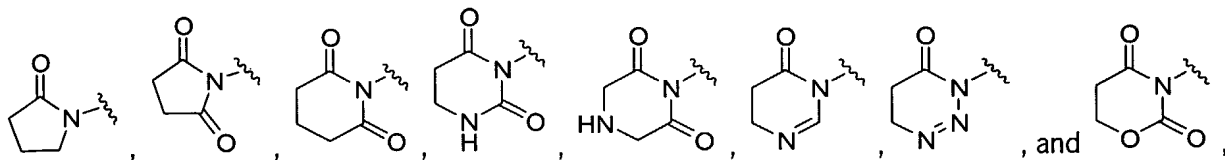
98. The compound according to claim 95 wherein Q at each occurrence is  $C(R^8)$ , where  $R^8$  is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy.
99. The compound according to claim 95 wherein from one to about three Q are nitrogen.
100. The compound according to claim 94 wherein  $Ar^3$  is selected from the group consisting of phenylene, pyridylene, thiazolylene, and quinolylene.
101. The compound according to claim 94 wherein  $X^2$  is a chemical bond.
102. The compound according to claim 94 wherein  $X^2$  is a non-cyclic hydrocarbyl.
103. The compound according to claim 94 wherein  $X^2$  is alkylene.
104. The compound according to claim 94 wherein  $X^2$  methylene or ethylene.
105. The compound according to claim 94 wherein  $X^2$  alkenylene or alkynylene.
106. The compound according to claim 102 wherein one carbon in the hydrocarbyl chain is replaced with -NH- or -S-.
107. The compound according to claim 94 wherein  $X^2$  is  $W^1-L^3-W^1$  and  $W^1$  is -NH- or -N(CH<sub>3</sub>)-.
108. The compound according to claim 94 wherein  $Cy^3$  is cycloalkyl.
109. The compound according to claim 94 wherein  $Cy^3$  is cyclohexyl.
110. The compound according to claim 94 wherein  $Cy^3$  is aryl or heteroaryl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
111. The compound according to claim 94 wherein  $Cy^3$  is phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.



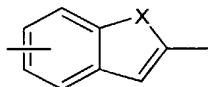
112. The compound according to claim 94 wherein the cyclic moiety of  $Cy^3$  is fused to a benzene ring.
113. The compound according to claim 94 wherein  $Cy^3$  has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl.
114. The compound according to claim 113 wherein the substituents are selected from methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl.
115. The compound according to claim 94 wherein  $Cy^3$  has from one to three substituents of the formula  $-K^1-N(H)(R^{10})$ , wherein  
 $K^1$  is a chemical bond or  $C_1-C_4$  alkylene;  
 $R^{10}$  is selected from the group consisting of  $Z'$  and  $-Ak^2-Z'$ , wherein  
 $Ak^2$  is  $C_1-C_4$  alkylene; and  
 $Z'$  is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings.
116. The compound according to claim 115 wherein the substituent is selected from



117. The compound according to claim 94 wherein  $Cy^3$  is heterocyclyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
118. The compound according to claim 94 wherein  $Cy^3$  is selected from

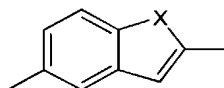


119. The compound according to claim 117 wherein the heterocycle of  $Cy^3$  is fused to a benzene ring.
120. The compound of claim 94 wherein when  $Ar^4$  is quinoxalinylenes, then  $X^3$  is not  $-CH(OH)-$ .
121. The compound of claim 94 wherein  $Ar^3$  is



and X is  $-CH_2-$ ,  $-NH-$ , O, or S.

122. The compound of claim 94 wherein  $Ar^3$  is



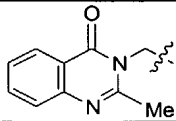
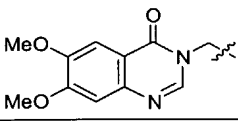
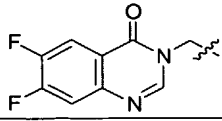
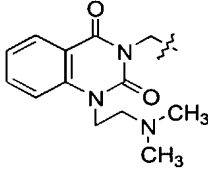
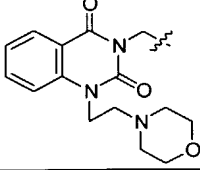
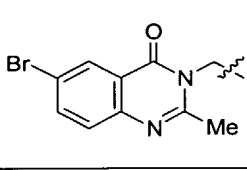
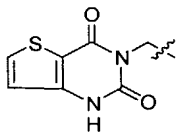
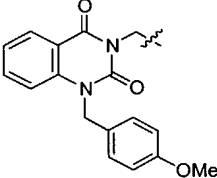
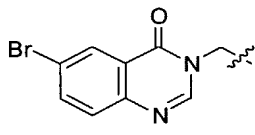
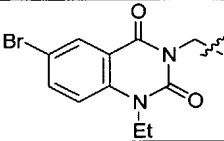
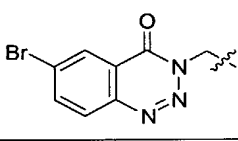
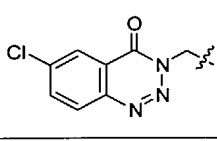
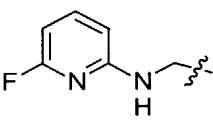
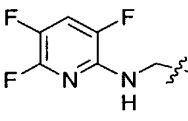
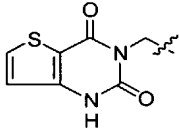
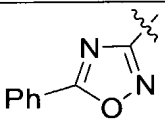
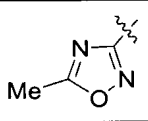
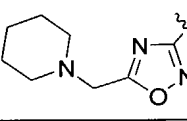
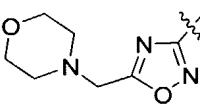
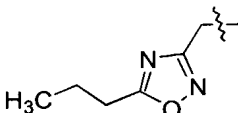
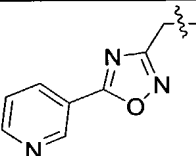
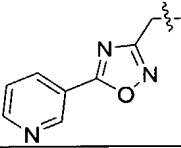
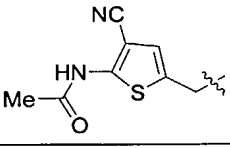
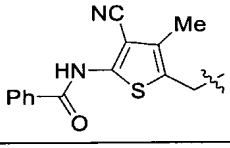
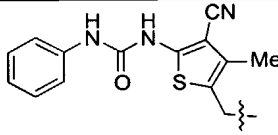
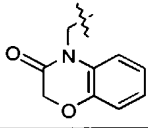
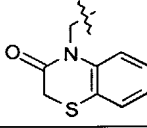
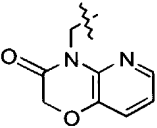
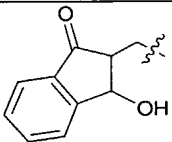
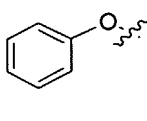
and X is S or O.

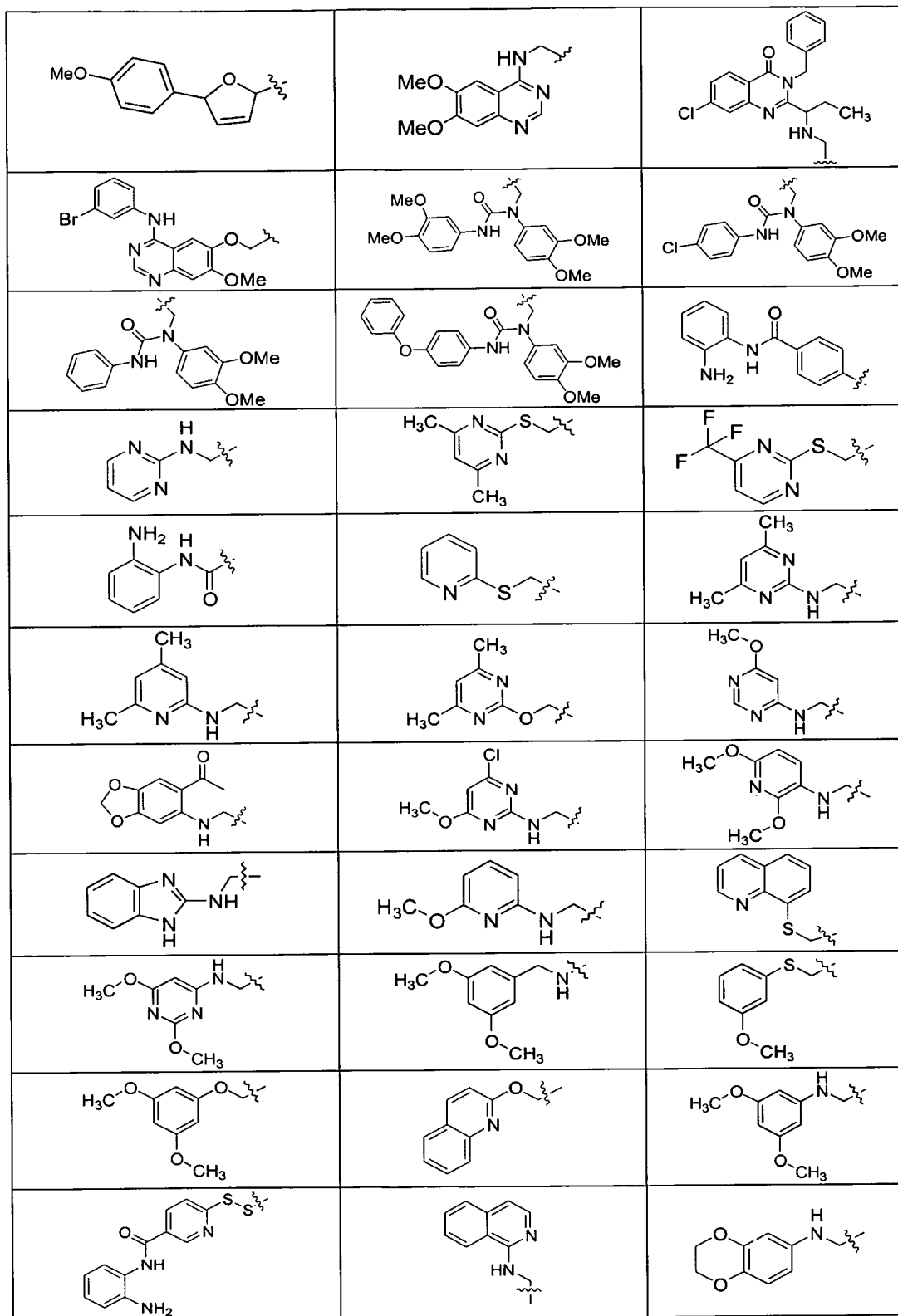
123. The compound according to claim 54 wherein  
 $Ay^2$  is ortho-anilinylenes;  
 q is 0; and  
 $X^1$  is  $M^1-L^2-M^1$  or  $L^2-M^2-L^2$ .
124. The compound according to claim 123 wherein  $Ar^2$  is aryl or heteroaryl; and  $Cy^2-X^1-$  is collectively selected from the group consisting of
- $A_1-L_1-B_1-$ , wherein  $A_1$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_1$  is  $-(CH_2)_{0-1}NH(CH_2)_{0-1}-$ ,  $-NHC(O)-$ , or  $-NHCH_2-$ ; and wherein  $B_1$  is phenyl or a covalent bond;
  - $A_2-L_2-B_2-$ , wherein  $A_2$  is  $CH_3(C=CH_2)-$ , optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein  $L_2$  is  $-C\equiv C-$ ; and wherein  $B_2$  is a covalent bond;

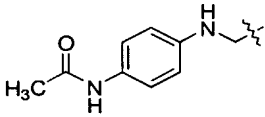
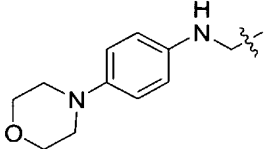
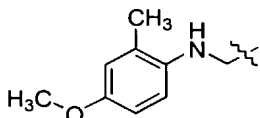
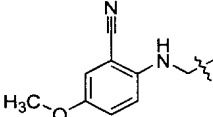
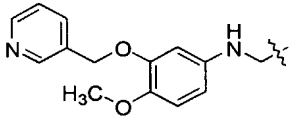
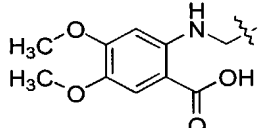
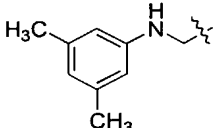
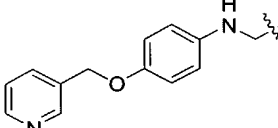
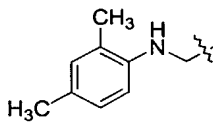
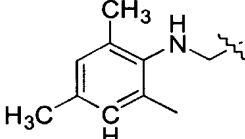
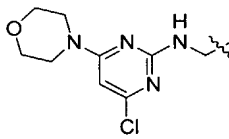
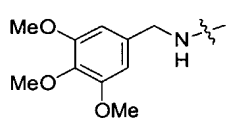
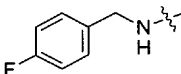
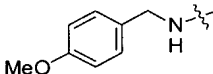
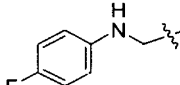
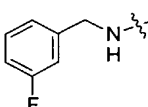
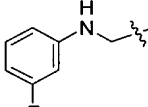
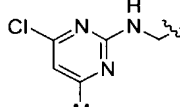
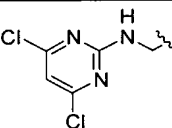
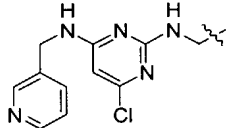
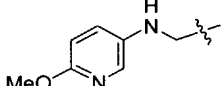
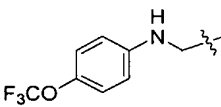
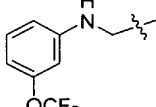
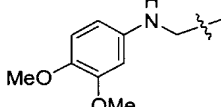
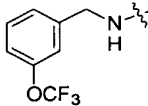
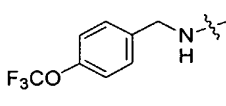
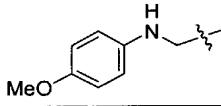
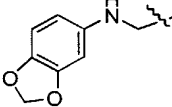
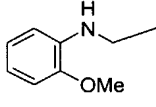
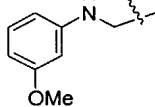
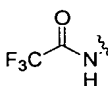
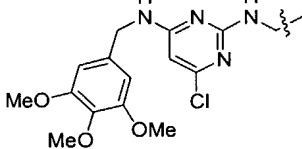
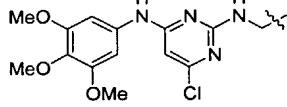
- c)  $A_3-L_3-B_3-$ , wherein  $A_3$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_3$  is a covalent bond; and wherein  $B_3$  is  $-CH_2NH-$ ;
- d)  $A_4-L_4-B_4-$ , wherein  $A_4$  is an optionally substituted aryl; wherein  $L_4$  is  $-NHCH_2-$ ; and wherein  $B_4$  is a thienyl group;
- e)  $A_5-L_5-B_5-$ , wherein  $A_5$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_5$  is a covalent bond; and wherein  $B_5$  is  $-SCH_2-$ ;
- f) morpholinyl- $CH_2-$
- g) optionally substituted aryl;
- h)  $A_6-L_6-B_6-$ , wherein  $A_6$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_6$  is a covalent bond; and wherein  $B_6$  is  $-NHCH_2-$ ;
- i)  $A_7-L_7-B_7-$ , wherein  $A_7$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_7$  is a covalent bond; and wherein  $B_7$  is  $-CH_2-$ ;
- j) optionally substituted heteroaryl or optionally substituted heterocyclyl;
- k)  $A_8-L_8-B_8-$ , wherein  $A_8$  is optionally substituted phenyl; wherein  $L_8$  is a covalent bond; and wherein  $B_8$  is  $-O-$ ;
- l)  $A_9-L_9-B_9-$ , wherein  $A_9$  is an optionally substituted aryl; wherein  $L_9$  is a covalent bond; and wherein  $B_9$  is a furan group;
- m)  $A_{10}-L_{10}-B_{10}-$ , wherein  $A_{10}$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{10}$  is  $-CH(CH_2CH_3)-$ ; and wherein  $B_{10}$  is  $-NHCH_2-$ ;
- n)  $A_{11}-L_{11}-B_{11}-$ , wherein  $A_{11}$  is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{11}$  is a covalent bond; and wherein  $B_{11}$  is  $-OCH_2-$ ;
- o)  $A_{12}-L_{12}-B_{12}-$ , wherein  $A_{12}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{12}$  is  $-NHC(O)-$ ; and wherein  $B_{12}$  is  $-N(\text{optionally substituted aryl})CH_2-$ ;
- p)  $A_{13}-L_{13}-B_{13}-$ , wherein  $A_{13}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{13}$  is a covalent bond; and wherein  $B_{13}$  is  $-NHC(O)-$ ;

- q)  $A_{14}$ - $L_{14}$ - $B_{14}$ -, wherein  $A_{14}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{14}$  is  $-NHC(O)(\text{optionally substituted heteroaryl})$ ; and wherein  $B_{14}$  is  $-S-S$ ;
  - r)  $F_3CC(O)NH$ -;
  - s)  $A_{15}$ - $L_{15}$ - $B_{15}$ -, wherein  $A_{15}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{15}$  is  $-(CH_2)_{0-1}NH(\text{optionally substituted heteroaryl})$ ; and wherein  $B_{15}$  is  $-NHCH_2$ ;
  - t)  $A_{16}$ - $L_{16}$ - $B_{16}$ -, wherein  $A_{16}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{16}$  is a covalent bond; and wherein  $B_{16}$  is  $-N(\text{optionally substituted alkyl})CH_2$ ; and
  - u)  $A_{16}$ - $L_{16}$ - $B_{16}$ -, wherein  $A_{16}$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $L_{16}$  is a covalent bond; and wherein  $B_{16}$  is  $-(\text{optionally substituted aryl-CH}_2)_2-N$ .
125. The compound according to claim 123 wherein  $Cy^2-X^1$ - is collectively selected from the group consisting of
- a)  $D_1-E_1-F_1$ -, wherein  $D_1$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_1$  is  $-CH_2$ - or a covalent bond; and wherein  $B_1$  is a covalent bond;
  - b)  $D_2-E_2-F_2$ -, wherein  $D_2$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_2$  is  $-NH(CH_2)_{0-2}$ ; and wherein  $F_2$  is a covalent bond;
  - c)  $D_3-E_3-F_3$ -, wherein  $D_3$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_3$  is  $-(CH_2)_{0-2}NH$ ; and wherein  $F_3$  is a covalent bond;
  - d)  $D_4-E_4-F_4$ -, wherein  $D_4$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_4$  is  $-S(CH_2)_{0-2}$ ; and wherein  $F_4$  is a covalent bond;
  - e)  $D_5-E_5-F_5$ -, wherein  $D_5$  is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein  $E_5$  is  $-(CH_2)_{0-2}S$ ; and wherein  $F_5$  is a covalent bond; and

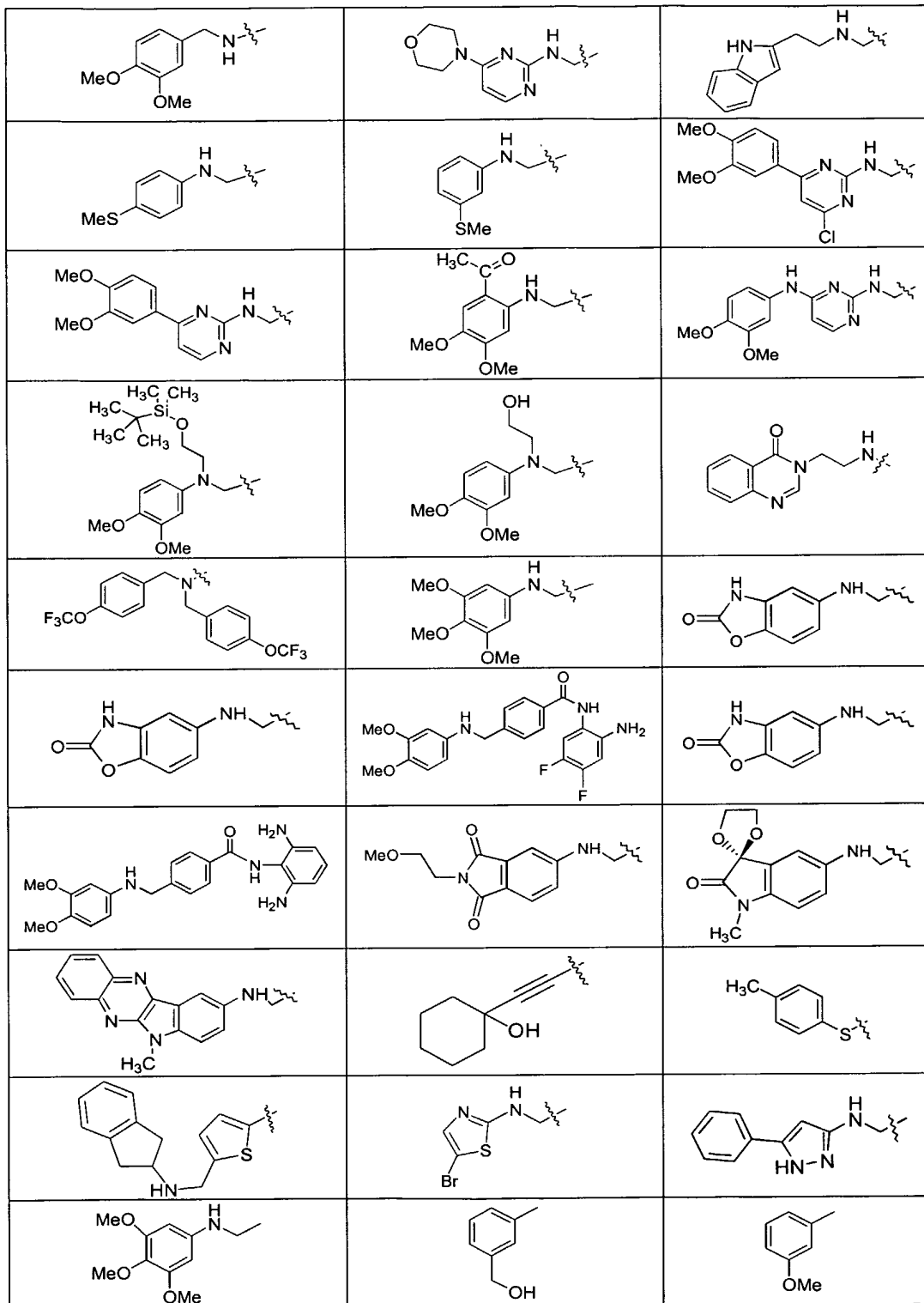


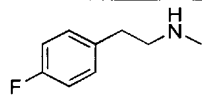

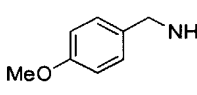
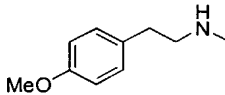
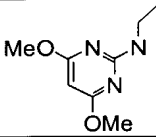
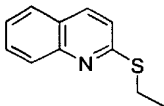
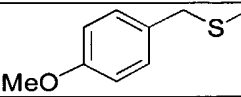
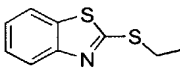
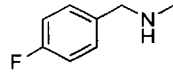
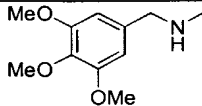
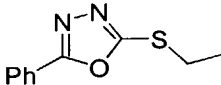
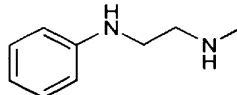
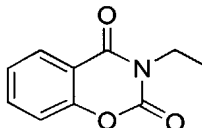
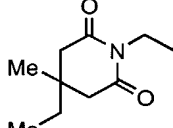
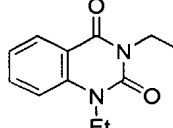
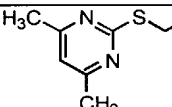
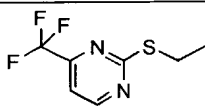
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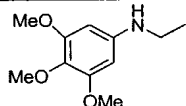
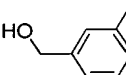
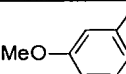
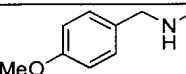
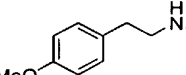
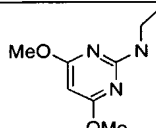
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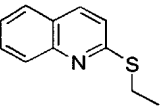
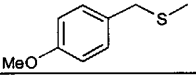
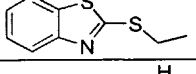
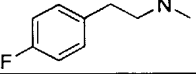
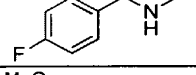
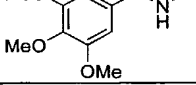
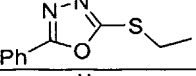
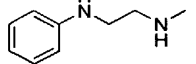


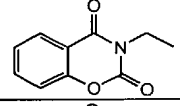
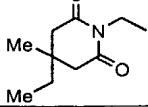
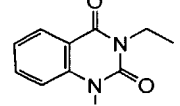
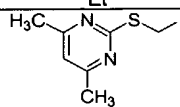
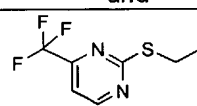


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|  | and   |  |

127. The compound according to claim 126 wherein Y, Z and W are one of the following combinations:

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 164 |  | CH | CH |
| 165 |  | N  | CH |
| 166 |  | CH | CH |
| 167 |  | CH | N  |
| 168 |  | CH | N  |
| 169 |  | CH | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 170 |  | CH | CH |
| 171 |  | N  | CH |
| 172 |  | CH | CH |
| 174 |  | CH | N  |
| 175 |  | CH | N  |
| 176 |  | CH | N  |
| 177 |  | CH | CH |
| 178 |  | N  | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 179 |  | CH | CH |
| 180 |  | CH | CH |
| 181 |  | CH | CH |
| 182 |  | CH | CH |
| and |   |    |    |
| 183 |  | CH | CH |

128. The compound according to claim 126 wherein Y, Z and W are one of the following combinations:

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 187 |   | CH | CH |
| 188 |   | CH | CH |
| 189 |   | CH | CH |
| 190 |   | CH | CH |
| 193 |   | CH | CH |
| 194 |   | CH | CH |
| 195 |   | CH | CH |
| 196 |   | CH | CH |
| 320 |   | CH | CH |
| 321 |   | CH | CH |
| 322 |   | CH | CH |
| 323 |   | CH | CH |

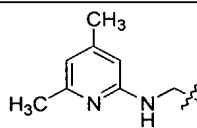
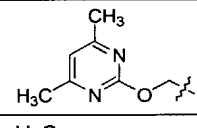
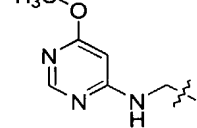
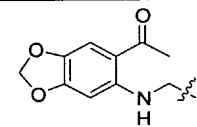
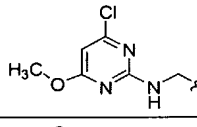
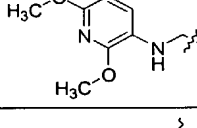
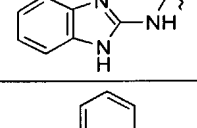
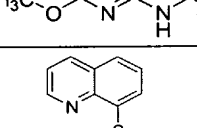
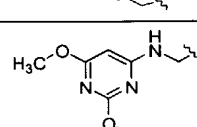
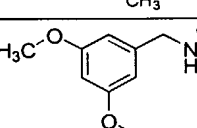
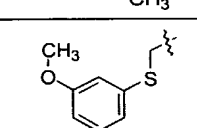

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 325 |   | CH | CH |
| 326 |   | CH | CH |
| 327 |   | CH | CH |
| 328 |   | CH | CH |
| 329 |   | CH | CH |
| 330 |   | CH | CH |
| 331 |   | CH | CH |
| 332 |   | CH | CH |
| 333 |   | CH | CH |
| 334 |   | CH | CH |
| 335 |   | CH | CH |

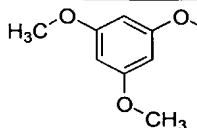
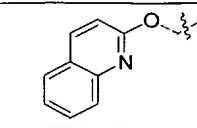
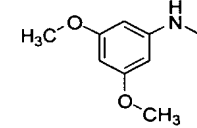
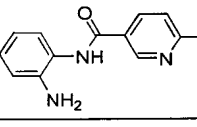
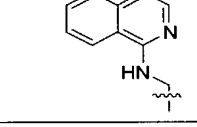
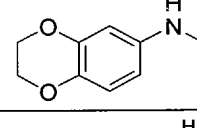
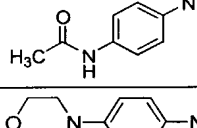
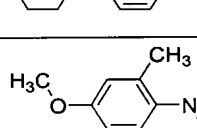
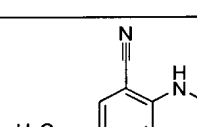
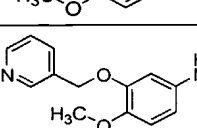
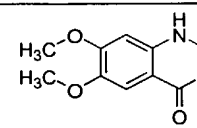

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 336 |   | CH | CH |
| 337 |   | CH | CH |
| 338 |   | CH | CH |
| 339 |   | CH | CH |
| 340 |   | CH | CH |
| 341 |   | CH | CH |
| 342 |   | CH | CH |
| 343 |   | CH | CH |
| 344 |   | CH | CH |
| 345 |   | CH | CH |
| 346 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 347 |   | CH | CH |
| 348 |   | CH | CH |
| 349 |   | CH | CH |
| 350 |   | CH | CH |
| 351 |   | CH | CH |
| 352 |   | CH | CH |
| 353 |   | CH | CH |
| 354 |   | CH | CH |
| 355 |   | CH | CH |
| 356 |   | CH | CH |
| 357 |   | CH | CH |
| 358 |   | CH | CH |
| 359 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 360 |   | CH | CH |
| 361 |   | CH | CH |
| 362 |   | CH | CH |
| 363 |   | CH | CH |
| 364 |   | CH | CH |
| 365 |   | CH | CH |
| 366 |   | CH | CH |
| 367 |   | CH | CH |
| 368 |   | CH | CH |
| 369 |   | CH | CH |
| 370 |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 371 |   | CH | CH |
| 372 |   | CH | CH |
| 373 |   | CH | CH |
| 374 |   | CH | CH |
| 375 |   | CH | CH |
| 377 |   | CH | CH |
| 378 |   | CH | CH |
| 379 |   | CH | CH |
| 380 |   | N  | CH |
| 381 |   | CH | CH |
| 382 |   | CH | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 383 |    | CH | CH |
| 384 |    | CH | CH |
| 385 |    | CH | CH |
| 386 |    | CH | CH |
| 387 |    | CH | CH |
| 388 |   | CH | CH |
| 389 |  | CH | CH |
| 390 |  | CH | CH |
| 391 |  | CH | CH |
| 392 |  | CH | CH |
| 393 |  | CH | CH |
| 394 |  | CH | CH |

| Cpd | W   | Y  | Z  |
|-----|---|----|----|
| 395 |    | CH | CH |
| 396 |    | CH | CH |
| 397 |    | CH | CH |
| 398 |    | CH | N  |
| 399 |    | CH | CH |
| 400 |   | CH | CH |
| 401 |  | CH | CH |
| 402 |  | CH | CH |
| 403 |  | CH | CH |
| 404 |  | CH | CH |
| 405 |  | CH | CH |
| 406 |  | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 407 |   | CH | CH |
| 408 |   | CH | CH |
| 409 |   | CH | CH |
| 410 |   | CH | CH |
| 411 |   | CH | CH |
| 412 |   | CH | CH |
| 413 |   | CH | CH |
| 414 |   | CH | CH |
| 415 |   | CH | CH |
| 416 |   | CH | CH |
| 417 |   | CH | CH |
| 418 |   | CH | CH |

| Cpd  | W | Y  | Z  |
|------|---|----|----|
| 419  |   | CH | CH |
| 420  |   | CH | CH |
| 421  |   | CH | CH |
| 422  |   | CH | CH |
| 423  |   | CH | CH |
| 424b |   | CH | CH |
| 425  |   | CH | CH |
| 426  |   | CH | CH |
| 427  |   | CH | CH |
| 428  |   | CH | CH |
| 429  |   | CH | CH |
| 430  |   | CH | CH |

| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 431 |   | CH | CH |
| 432 |   | CH | CH |
| 433 |   | CH | CH |
| 434 |   | CH | CH |
| 435 |   | CH | CH |
| 436 |   | CH | CH |
| 437 |   | CH | CH |
| 438 |   | CH | CH |
| 439 |   | CH | CH |
| 440 |   | CH | CH |
| 441 |   | CH | CH |

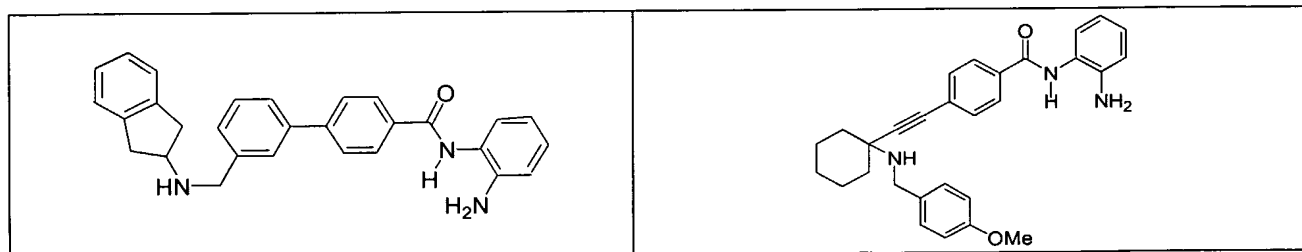
| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 442 |   | CH | CH |
| 443 |   | CH | CH |
| 444 |   | CH | CH |
| 445 |   | CH | N  |
| 446 |   | CH | N  |
| 447 |   | CH | CH |
| 448 |   | CH | CH |
| 449 |   | CH | CH |
| 450 |   | CH | CH |
| 451 |   | CH | CH |
| 452 |   | CH | CH |
| 453 |   |    |    |

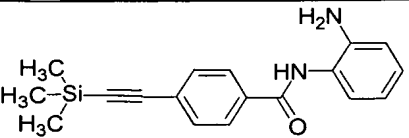
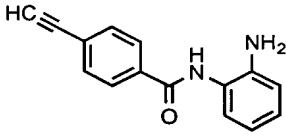
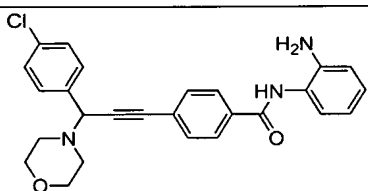
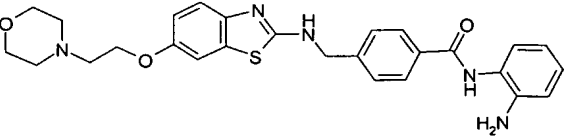
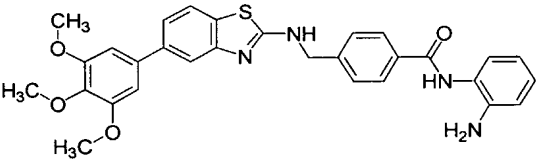
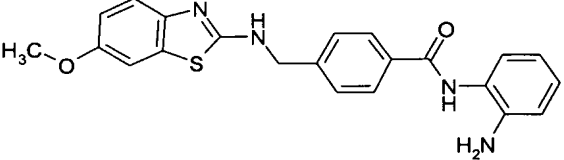
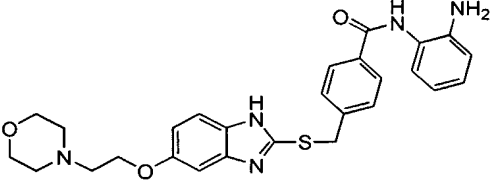
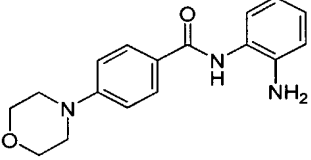
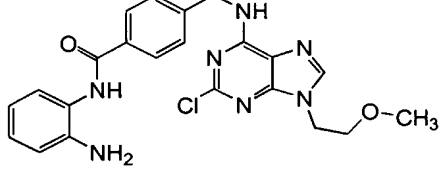
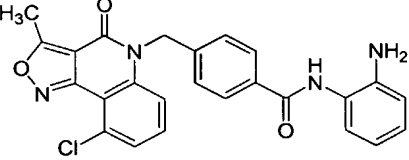
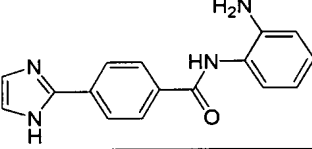
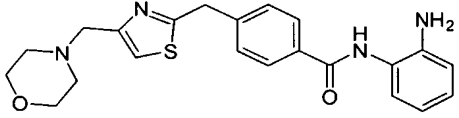
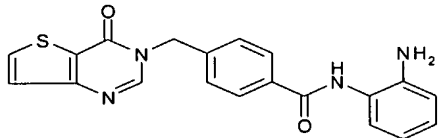
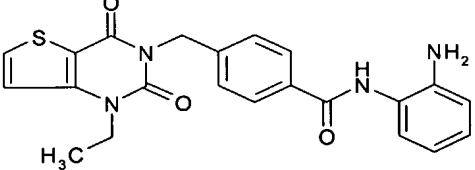
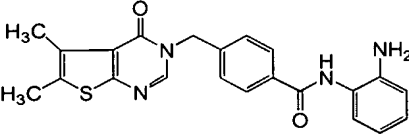
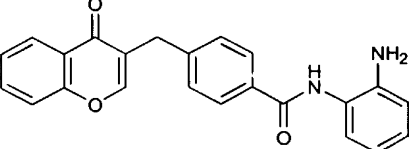


| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 454 |   |    |    |
| 455 |   | CH | CH |
| 456 |   | CH | CH |
| 457 |   |    |    |
| 458 |   | CH | CH |
| 459 |   | CH | CH |
| 460 |   | CH | N  |
| 461 |   | CH | CH |

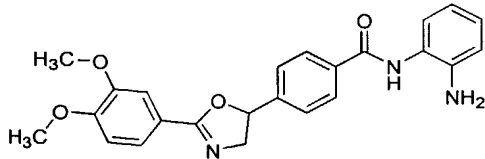
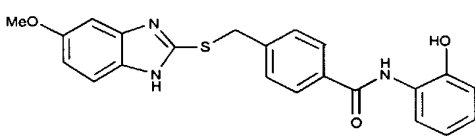
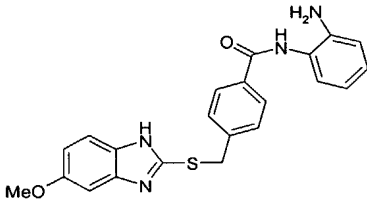
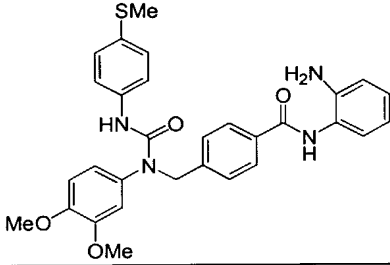
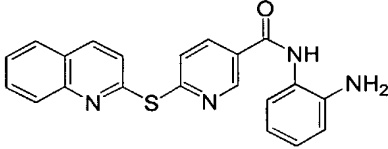
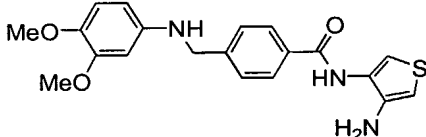
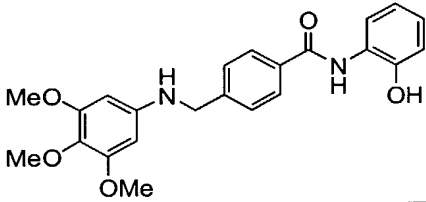
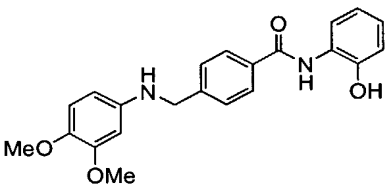
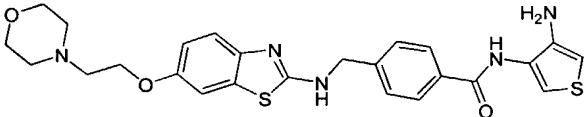
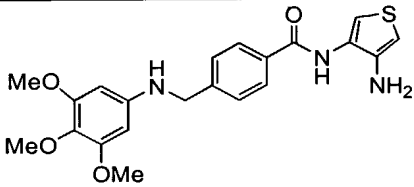
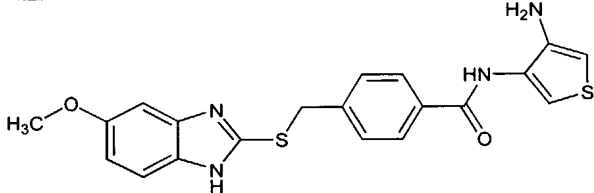
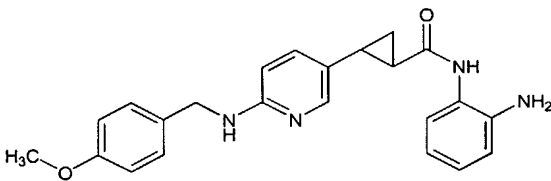
| Cpd | W | Y  | Z  |
|-----|---|----|----|
| 462 |   | CH | CH |
| 463 |   | N  | CH |
| 464 |   | N  | CH |
| 465 |   | CH | CH |
| 466 |   | CH | CH |
| 467 |   | CH | CH |
| 468 |   | CH | CH |

129. A compound selected from the group consisting of the following and their pharmaceutically acceptable salts:



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130. A histone deacetylase inhibitor selected from the compounds listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f, or a pharmaceutically acceptable salt thereof.
131. A composition comprising a compound according to any one of claim 1-130 and a <sup>\*</sup> pharmaceutically acceptable carrier.
132. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a compound according to any one of claim 1-130.

Antitumor Activity of MethylGene Small Molecule HDAC Inhibitors in HCT116 Human  
Colorectal Tumor Model

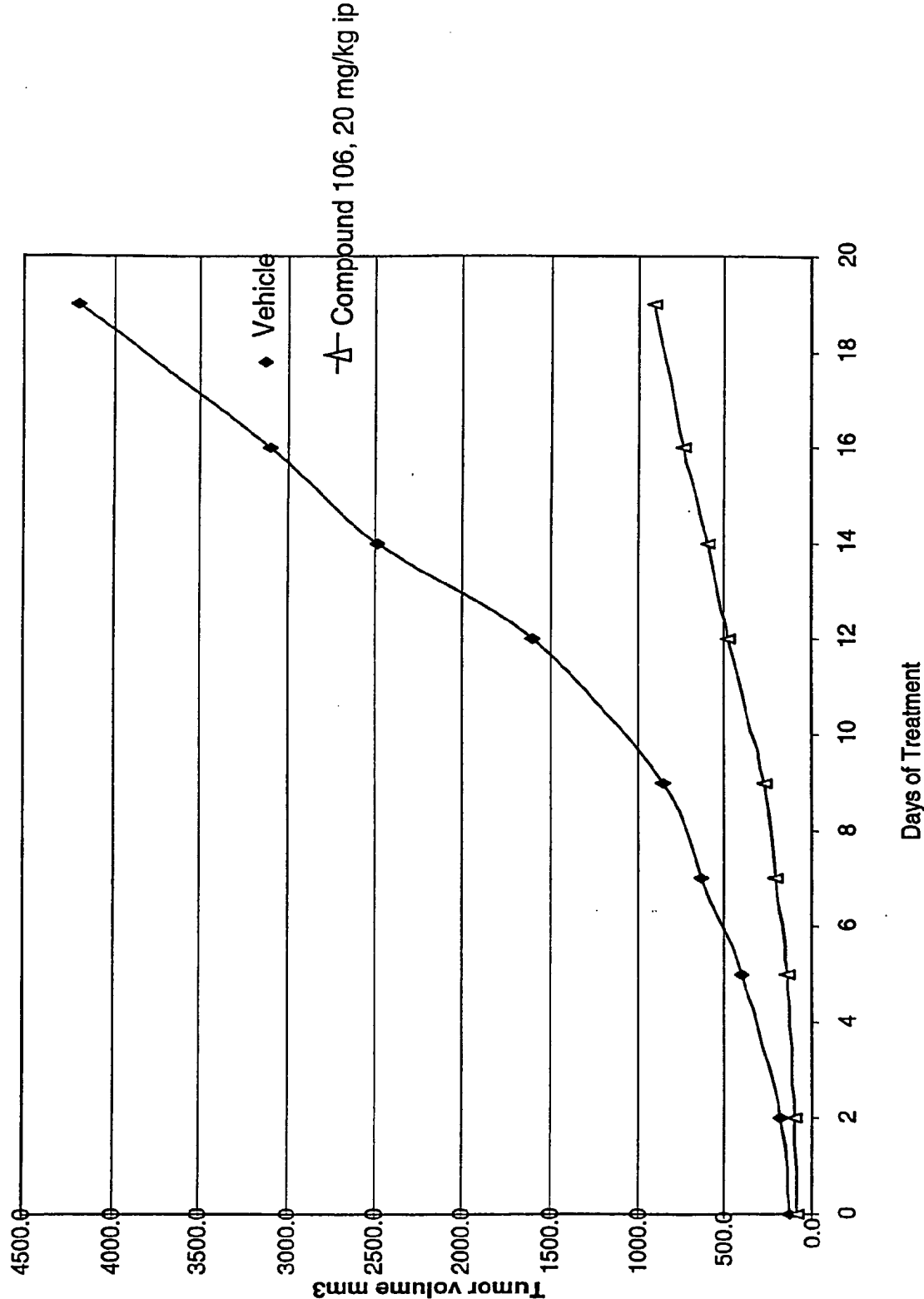


FIG. 1

Inhibition of A549 Human Lung Cancer Tumor Growth by  
Compound 106 After Intraperitoneal Administration

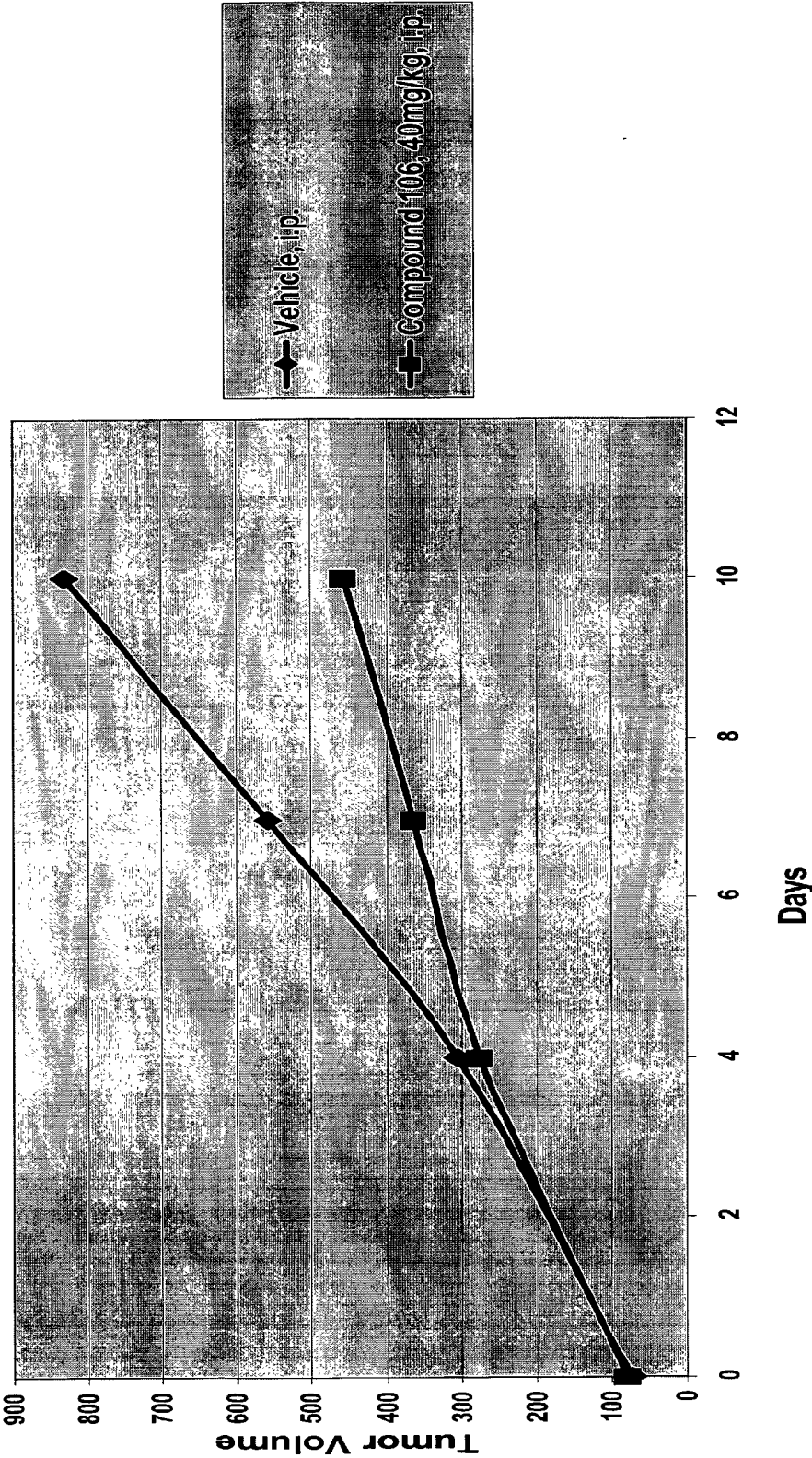
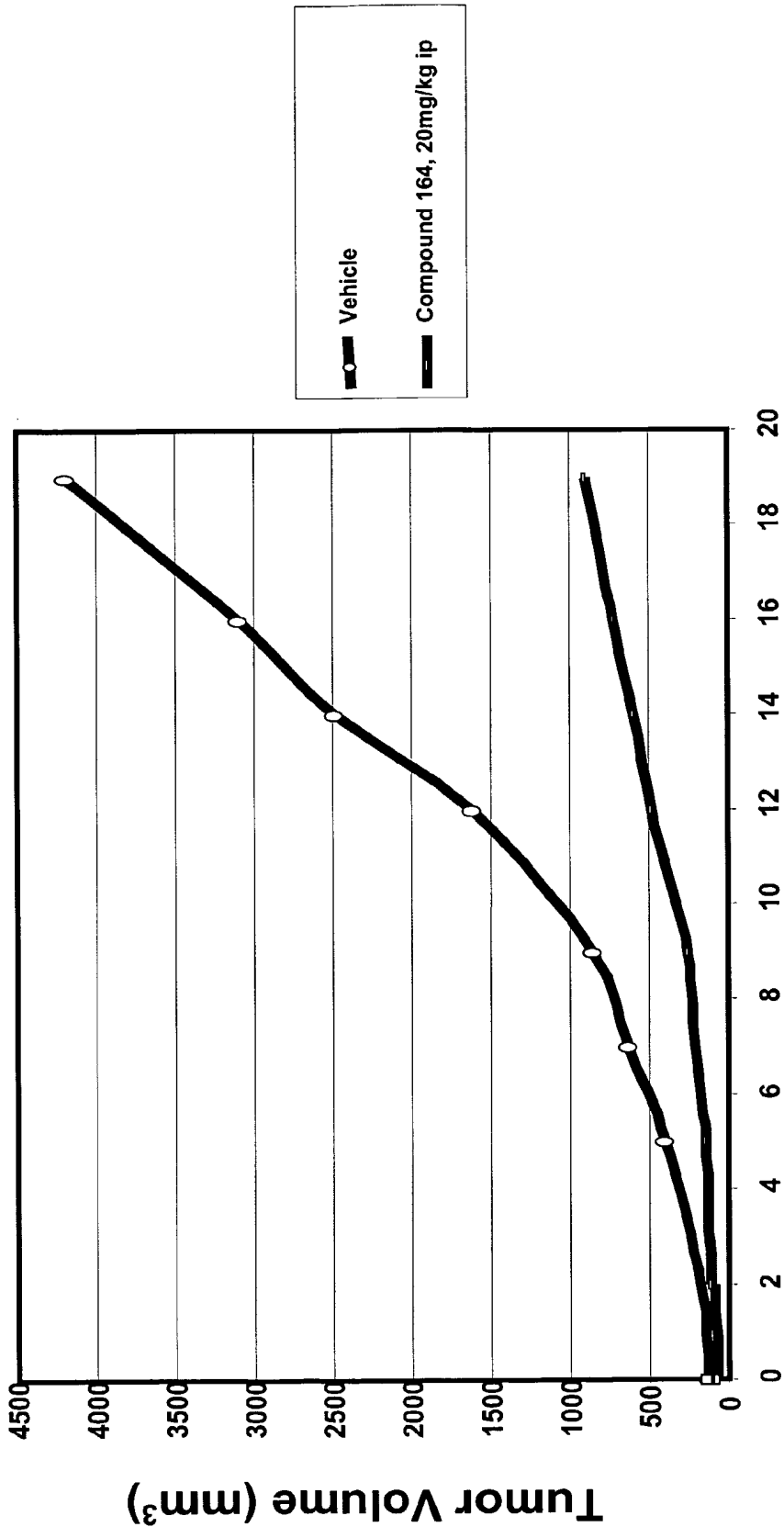


Fig. 2

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 164  
after Intraperitoneal Administration



Days of Treatment

Fig. 3

**Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth  
by Compound 228 After Oral Administration**

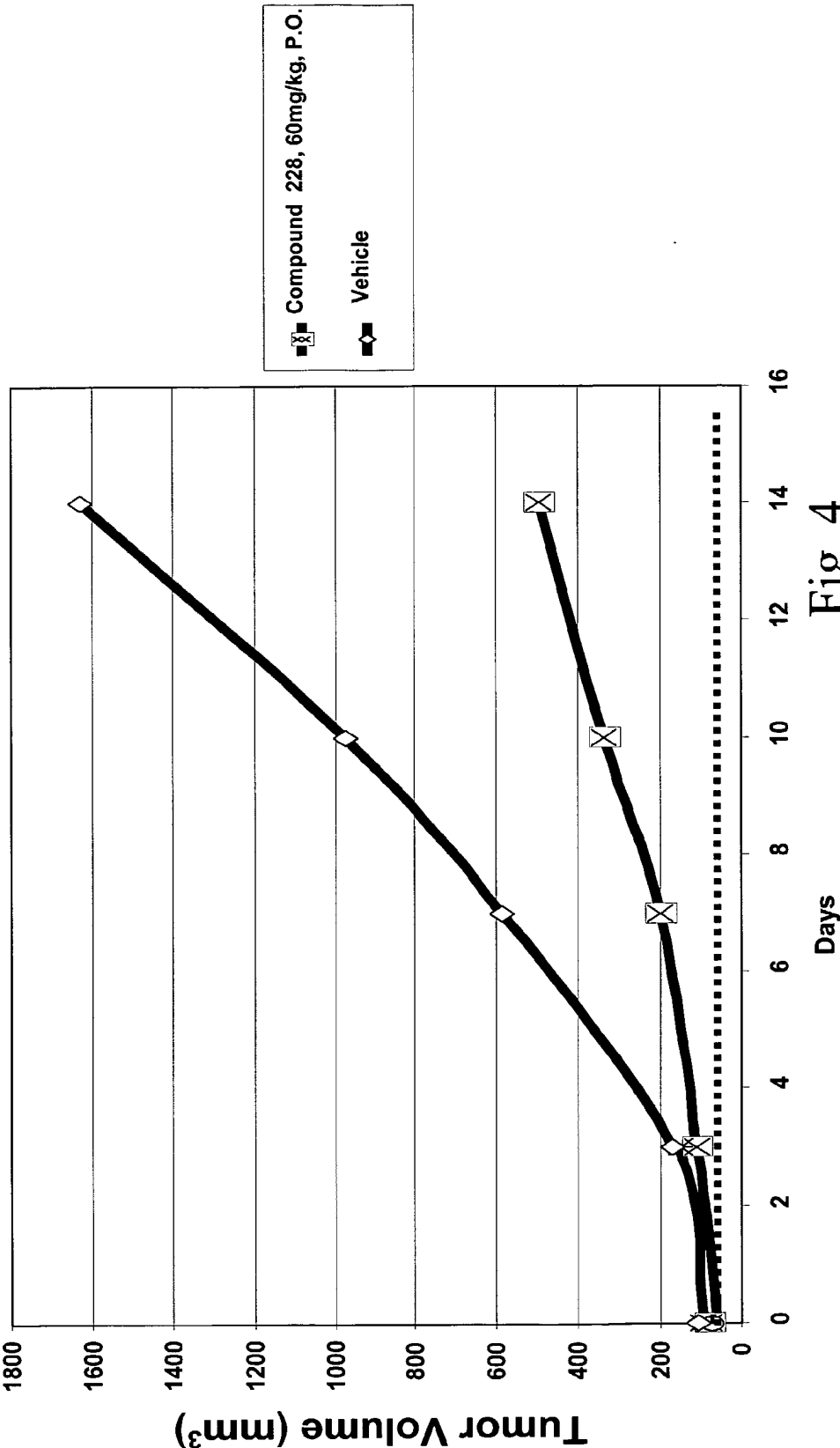


Fig. 4



# Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 311 after Intraperitoneal Administration

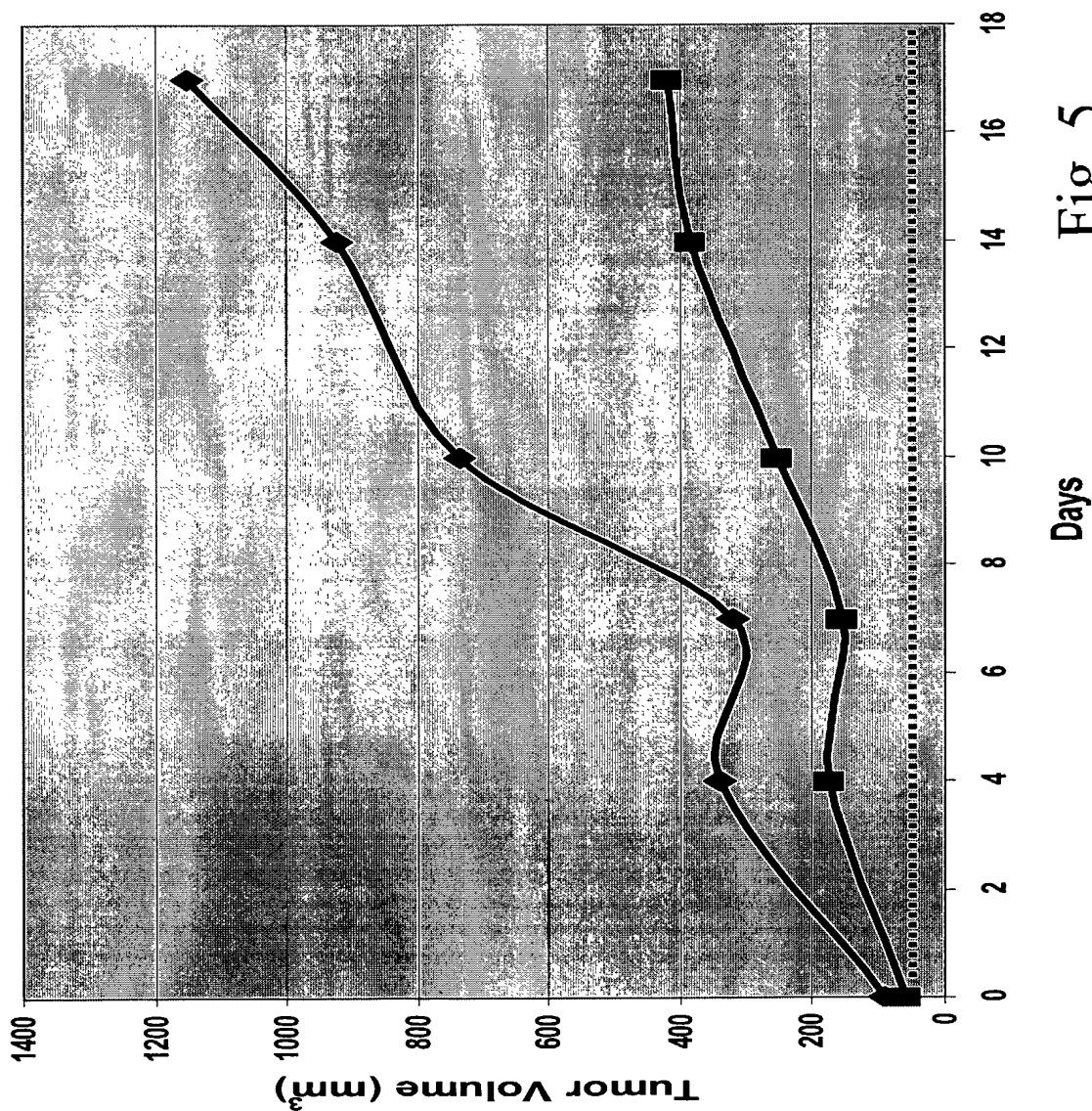
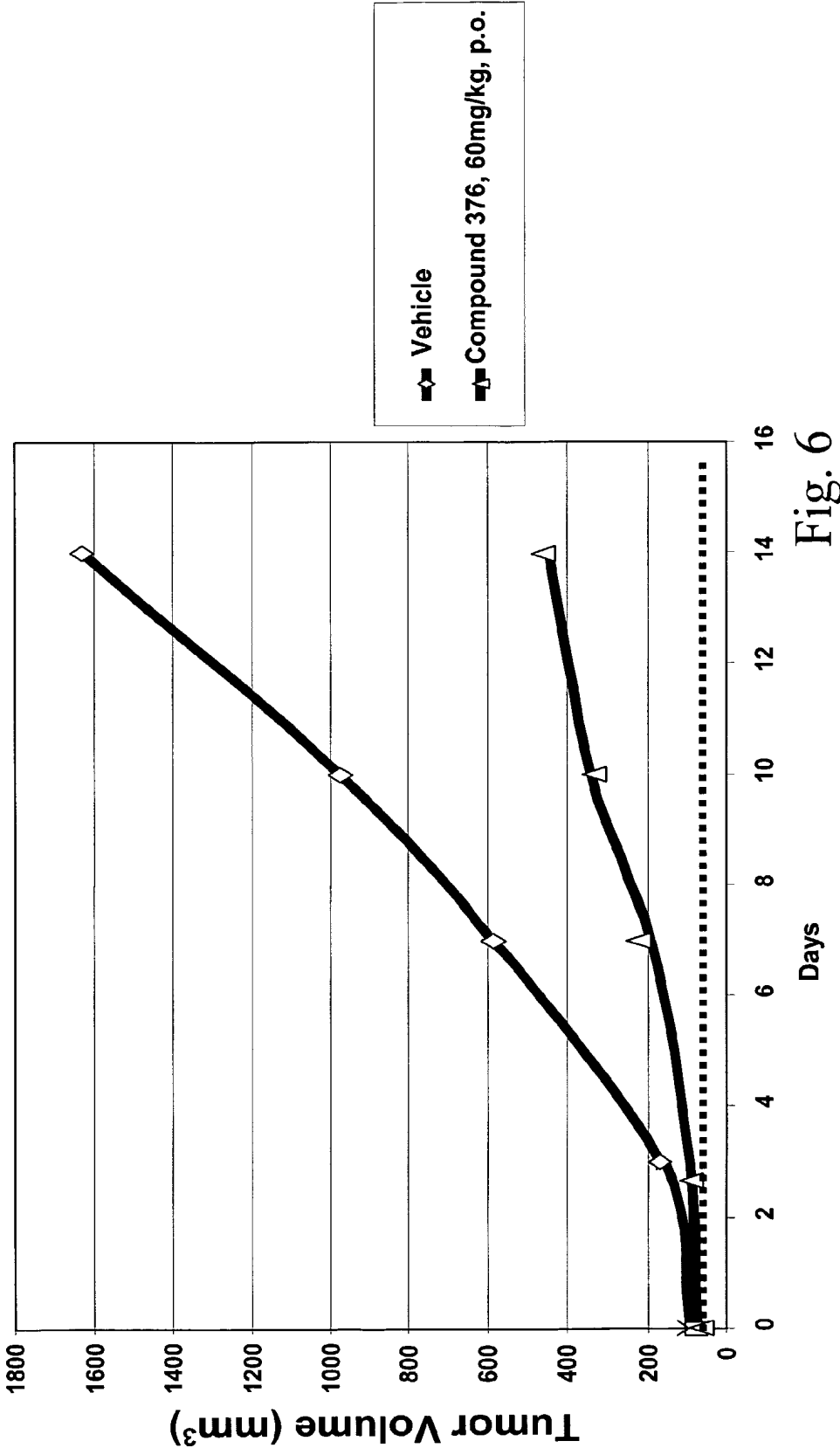
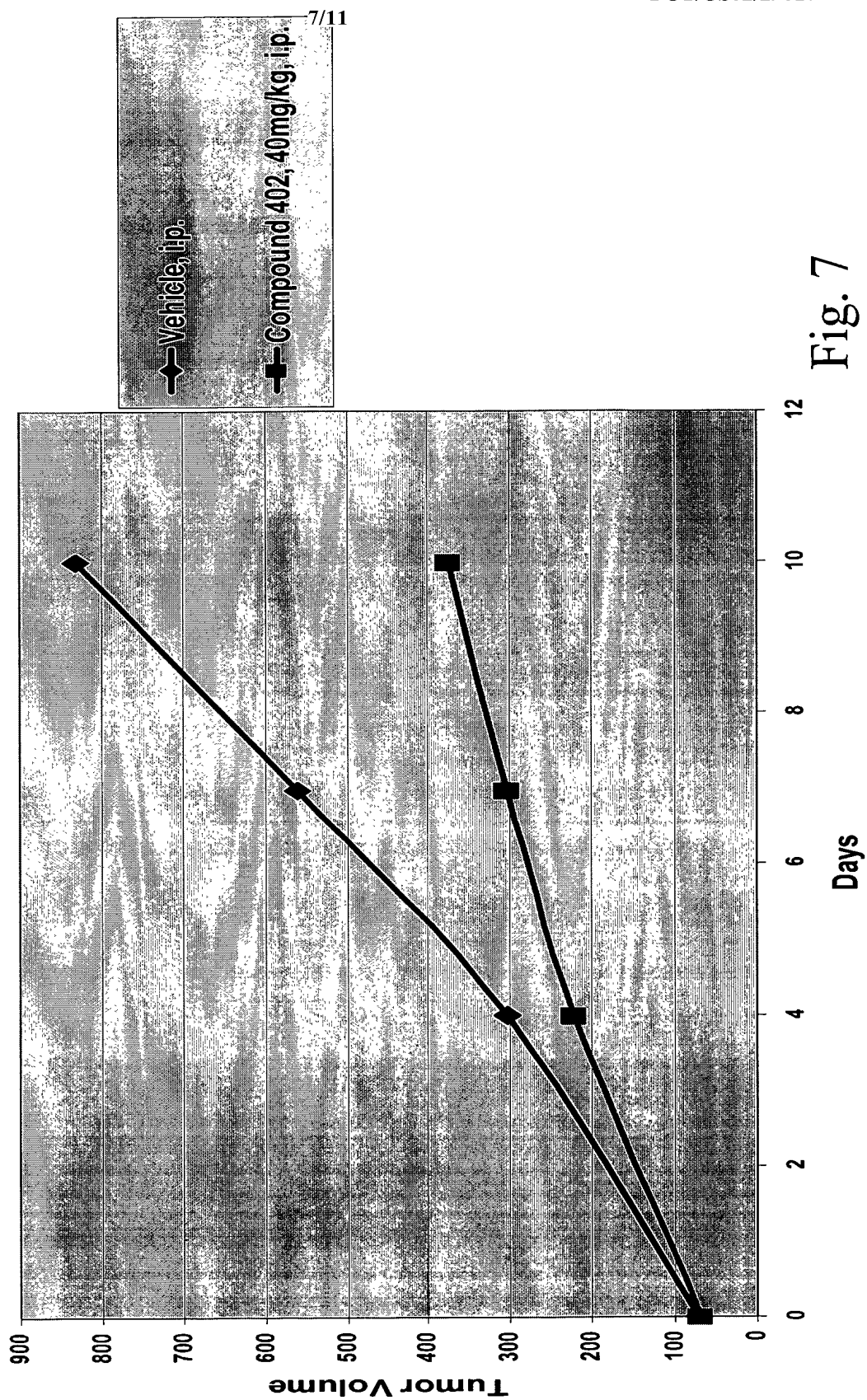


Fig. 5

**Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth  
by Compound 376 After Oral Administration**



# Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 402 After Intraperitoneal Administration



# Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 421 After Oral Administration

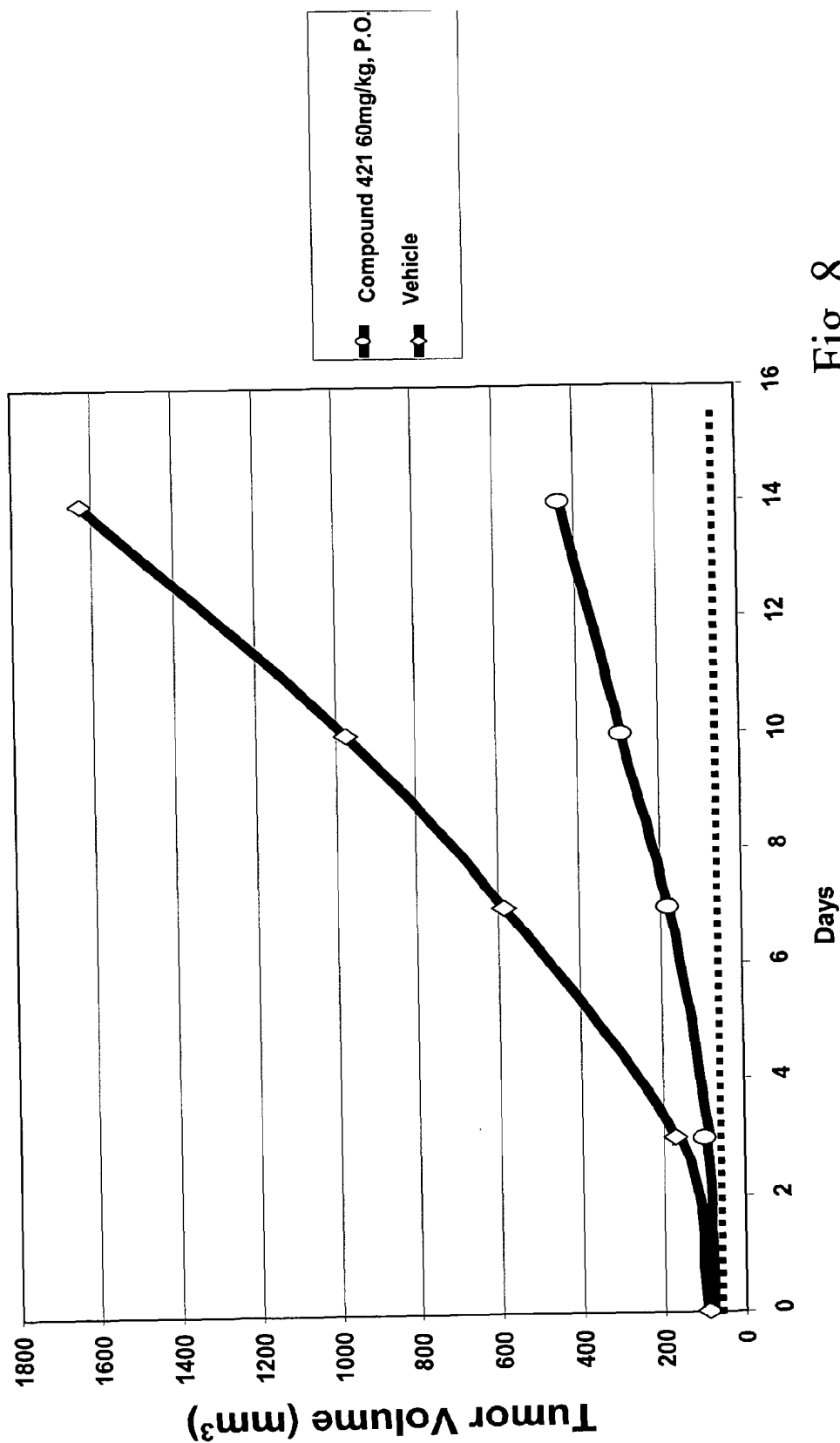


Fig. 8

# Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Intraperitoneal Administration

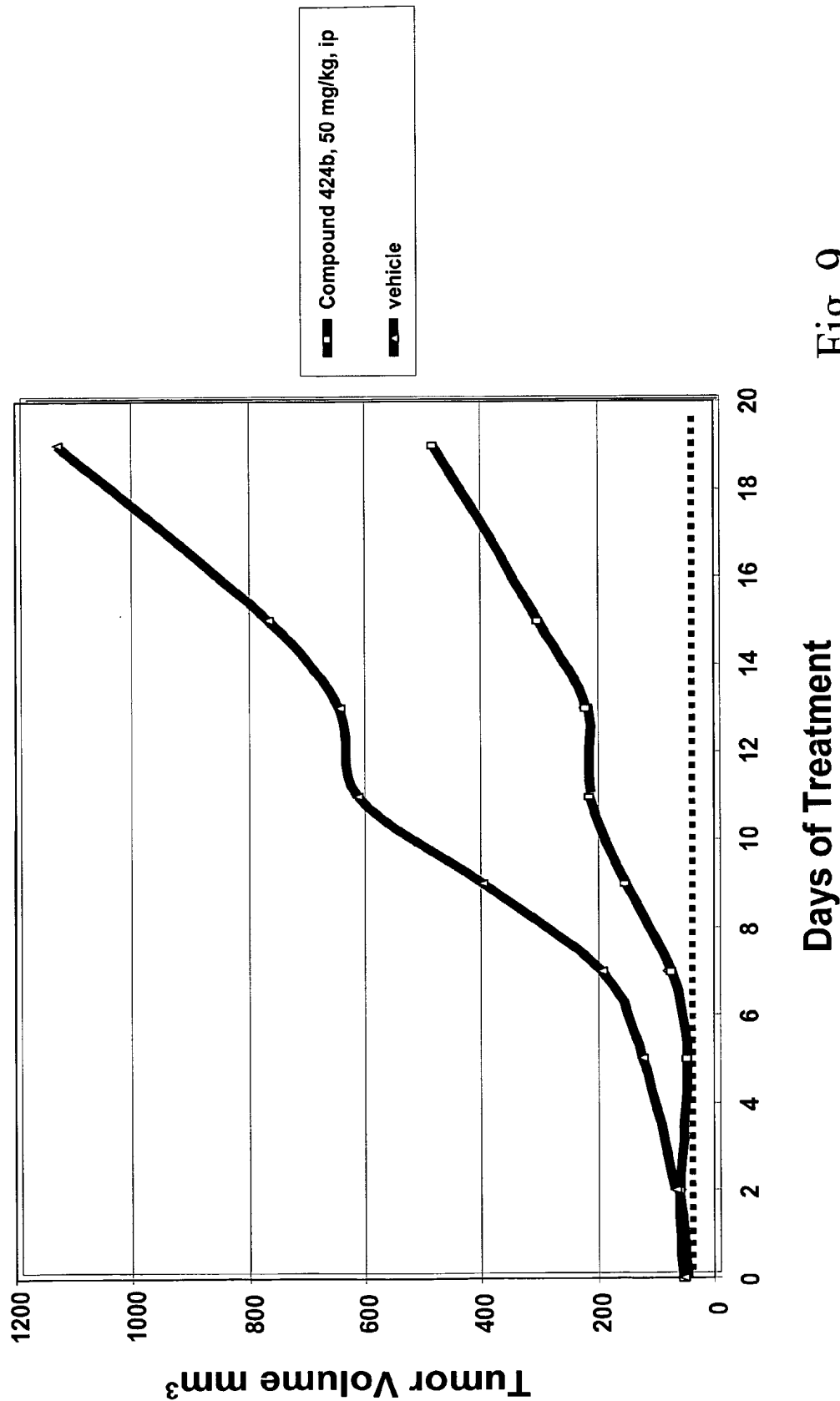
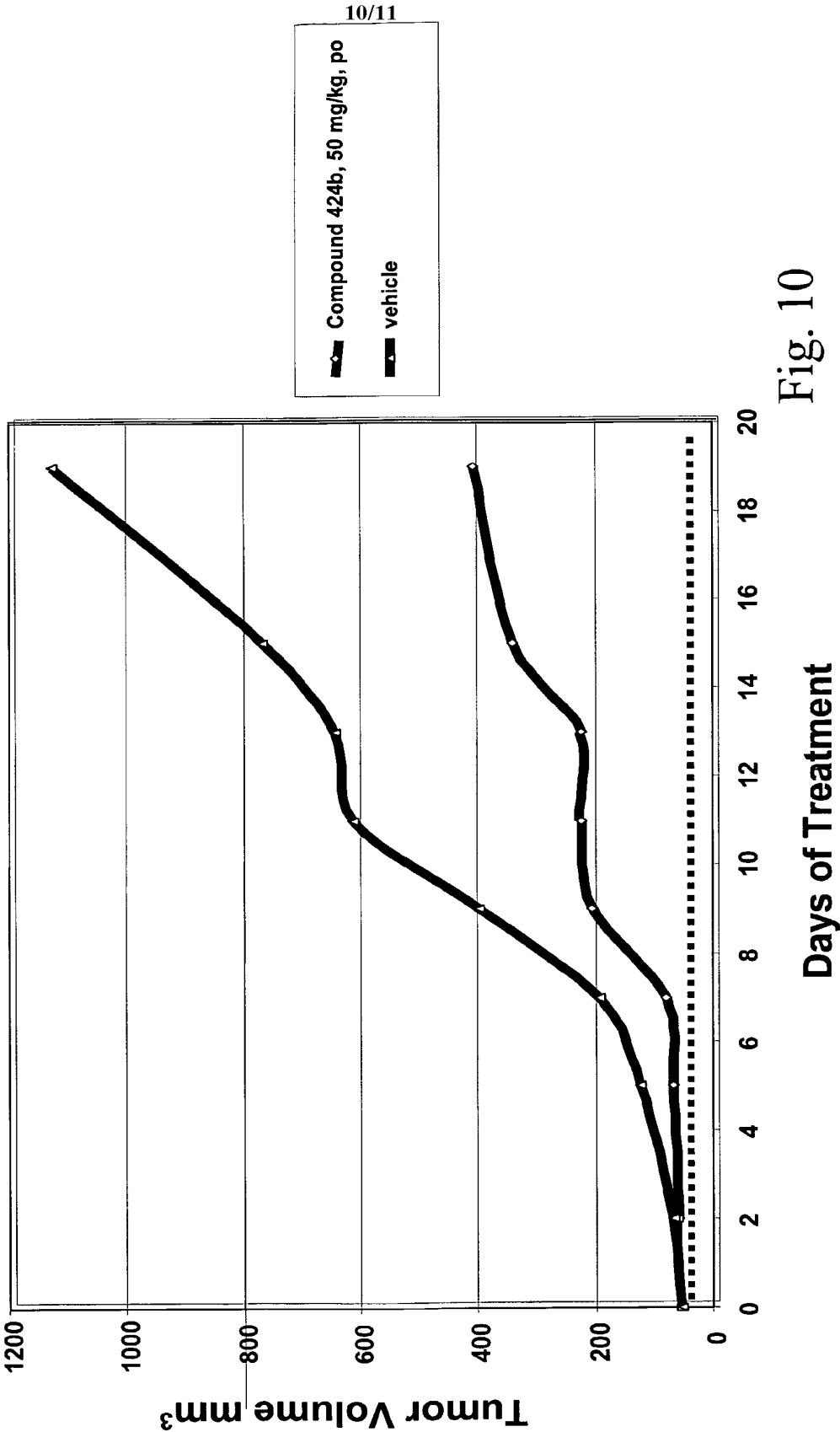


Fig. 9

Inhibition of A549 Human Lung Cancer Tumor Growth by  
Compound 424b after Oral Administration



Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 570 after Intraperitoneal Administration

